March 2006

Final Honours Thesis in Psychology

Cognitive change in motor neurone disease:

Evidence of orbitofrontal dysfunction.

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Colin designed the computer program used to administer the Visual Discrimination Learning Task in this study.

Contents

Abstract

This study examines the presence of cognitive changes in amyotrophic lateral sclerosis (ALS), a subtype of motor neurone disease. Past research has shown executive dysfunction in patients with ALS and frontotemporal dementia (FTD). A minority of ALS patients without FTD also show some cognitive changes, however the role of the orbitofrontal cortex (OFC) in this patient group has not been investigated. OFC damage can lead to perseveration and behaviour change. The performance of a group of 10 patients with ALS and 10 matched controls was compared on series of cognitive tests known to be sensitive to OFC damage. Two tests of punishment/reward contingency learning were used: the Iowa Gambling Task and our own task based on a previous study of individuals with OFC damage, which requires quickly switching from one rule to a newly learnt rule. A Theory of Mind task known to be sensitive to changes in FTD, the Faux Pas Test was also used. Cognitive tests also included a test of written verbal fluency and a test of confrontation naming ability, as ALS patients have previously shown deficits on these tests. This study did not find any significant group differences, however several patients were outside the normal range of scores for control participants on the three measures sensitive to OFC dysfunction. These results are discussed in relation to relevant research regarding orbitofrontal dysfunction and methodological improvements are suggested. It is concluded that cognitive changes in ALS non dementia can involve orbitofrontal dysfunction and that these changes can occur without concomitant changes affecting written verbal fluency and confrontation naming ability.

Introduction

Motor neurone disease

Motor neurone disease (MND) is a degenerative and terminal condition affecting upper motor neurones in the brain, mainly cerebral cortex and brainstem, and lower motor neurones in the spinal cord (Abrahams et al., 1997; Abrahams et al., 2000; Brooks, Miller, Swash & Munsat,

1998; Rolls, Hornak, Wade & McGrath, 1994). MND is characterised by motor dysfunction in the limbs and/or bulbar areas but also in abdominal and thoracic muscles (Leigh & Ray-Chaudhuri, 1994), consequently areas with affected motor neurons show fasciculations and atrophy due to a lack of voluntary movement. A quarter of cases show bulbar onset and three quarters show limb onset (Abrahams & Goldstein, 2002; Leigh & Ray-Chaudhuri, 1994). Onset of MND is more likely in mid or later life and onset is most likely between the ages of 60 and 70 (Abrahams & Goldstein, 2002; Leigh & Ray-Chaudhuri, 1994). Death generally occurs within five years, although mortality can vary with ethnicity: white South Africans, Mexicans and Asian immigrants to the UK have been found to show a lower mortality rate than the general population of the UK (Abrahams & Goldstein, 2002; Leigh & Ray-Chaudhuri, 1994). Death is commonly from asphyxiation due to respiratory failure, therefore bulbar onset or bulbar symptoms give a poorer prognosis (Leigh & Ray-Chaudhuri, 1994). MND is of unclear aetiology and is diagnosed by excluding other possible explanations for symptoms shown in an individual that are consistent with MND (Abrahams et al. 2000; Brooks et al., 1998; Leigh & Ray-Chaudhuri, 1994).

Prevalence, incidence and genetics factors

MND has a sex ratio of three:two male to female ratio and is sporadic in 90 to 95 percent of cases with an incidence of one to two people per 100,000 and a prevalence of four to six per 100,000 (Abrahams & Goldstein, 2002; Leigh & Ray-Chaudhuri, 1994). In five to 10 percent of cases, MND is hereditary and the genes responsible for these hereditary cases are dominant, the main genetic variant identified so far is superoxide dismutase one (SOD1) (Abrahams & Goldstein, 2002; Brooks et al., 1998).

Amyotrophic lateral sclerosis

Several subtypes of MND have been identified, the most common being amyotrophic lateral sclerosis (ALS). The most recently agreed criteria for the diagnosis of ALS have been proposed by Brooks et al. (1998). In summary these criteria are as follows: for sporadic cases of ALS and

hereditary cases not linked to SOD1 there must be clinical evidence of both lower motor neurone (LMN) and upper motor neurone (UMN) degeneration, accompanied by evidence of progressively spreading symptoms (Brooks et al., 1998). Exclusion criteria include lack of neuroimaging evidence suggesting an alternative diagnosis, and a lack of pattern and electrophysiological evidence that could account for the upper and/or lower motor neurone symptoms (Brooks et al., 1998). For a diagnosis of ALS in hereditary cases linked to SOD1, it is only necessary to identify a UMN or LMN signs in one region (Brooks et al., 1998). For the purposes of this study the term ALS shall be used to refer to the condition affecting our participants and previous research where applicable as it provides a more focused definition than the general category of MND.

Cognitive changes

Individuals with MND and Frontotemporal Dementia (FTD) may exhibit some cognitive and behaviour changes, including cognitive deficits in controlling changes of attention, written verbal fluency, facial recognition, visual perception, abstract problem solving and reasoning (Abrahams et al., 2005; Barson, Kinsella, Ong, & Mathers, 2000; Strong et al., 1999). Behavioural changes have been observed in generating and inhibiting responses, planning, behavioural monitoring and awareness, though there is not a complete lack of inhibition (Barson et al., 2000; Bechara et al., 2000). There is also some evidence of working memory deficits, particularly on novel tasks (Barson et al., 2000; Strong et al., 1999). Some of these cognitive changes observed have been associated with damage to the orbitofrontal cortex (OFC) (O'Doherty et al., 2001). In 25 to 50 percent of cases of ALS there are some subtle cognitive changes, which tend to be confined to, or most noticeable in, areas of the executive functions (Abrahams, Goldstein & Leigh, 2005; Leigh & Ray-Chaudhuri, 1994; Rolls et al., 1994). Some cognitive changes may not be obvious either to carers or to the patients themselves, as individuals with ALS tend to have diminishing responsibility in planning and carrying out their own activities since the condition is progressively debilitating (Abrahams et al., 2005). Cognitive changes observed in cases of ALS

are similar to those seen in cases where ALS occurs along with FTD, this is present in approximately three percent of sporadic ALS cases (Abrahams & Goldstein, 2002; Abrahams et al., 2005; Rolls et al., 1994). It is not clear if ALS patients with cognitive changes form a separate subgroup, or if there is a continuum between those with ALS who show slight cognitive changes and those with ALS and FTD (Abrahams et al., 2005).

Written Verbal Fluency Index

One of the most consistently demonstrated cognitive changes shown in non dementia patients with ALS is a deficit on tests of written verbal fluency (WVF). These tests have conventionally been used in evaluating executive dysfunction. A series of studies have found that some individuals with ALS show poorer performance than control participants on WVF tests (Abrahams et al., 1997; Abrahams et al., 1996; Abrahams et al., 2005; Abrahams et al., 2000). WVF tends to be impaired early on in the progress of ALS (Abrahams et al., 2005). Tests of WVF involve writing a list of words beginning with a given letter of the alphabet in a specified period of time and with certain constraints. WVF tasks are thought to measure the speed of internal response generation or "thinking time" (Abrahams et al., 1997; Abrahams et al., 2000). Traditionally WVF tests such as the Thurston Word Fluency Test have been used, however these do not take account of variation in writing speed between individuals (Thurstone & Thurstone, 1962, as cited in Abrahams et al., 2005). The effect of writing speed is of particular relevance when testing individuals with ALS, as the disease tends to slow down most individuals' writing speed compared to their pre-morbid performance and the performance of control participants. More recently, WVF tasks have been adapted to calculate a Written Verbal Fluency Index (WVFI), which factors out the effect of writing speed and gives a pure measure of thinking time, allowing a more accurate comparison between individuals with ALS and control groups (Abrahams et al., 2000). Abrahams et al. (2005) suggest from an analysis of the cognitive basis of written verbal fluency that the deficit that can be observed is not caused by a phonological loop deficit or by a deficit in primary language function of simple word retrieval but rather that the

basis for the observed deficits on written verbal fluency are caused by higher level executive functions responsible for intrinsic response generation (Abrahams et al., 2005; Abrahams et al., 2000; Baddeley & Logie, 1999). Furthermore, Abrahams et al. (2005) found that patients performed worse than controls on the WVFI, but they did not find any deterioration in the patients' performance after six months. They suggest that this WVFI deficit is likely to deteriorate slowly in spite of its occurrence early on in the progress of ALS.

Various studies have proposed anatomical correlates for this WVFI deficit (Abrahams et al., 1997; Abrahams et al., 1996; Abrahams et al. 2000), the most frequently identified area being the dorso-lateral pre-frontal cortex (DLPFC). Abrahams et al. (2000) claim that the selective cognitive impairments revealed by the WVFI are typical of extra motor cerebral dysfunction and that their profile of impairment is consistent with imaging evidence suggesting that the difficulties experienced by some ALS patients without dementia may be due to damage of the DLPFC. Abrahams et al. (1997) note that positron emission tomography (PET) studies of ALS patients have shown reduced regional cerebral blood flow (RCBF) in the left DLPFC during verbal fluency tasks. Abrahams et al. (1996) found that RCBF was similar between controls and ALS patients who did not show a deficit on the WVFI, whereas patients who performed poorly on the WVFI showed diminished DLPFC activation compared to the control group and normally performing members of the ALS group.

Summary of cognitive measures on which ALS patients have shown deficits.

In addition to deficits of written verbal fluency, ALS patients have shown poor performance on many common neuropsychological tests of cognitive function and memory. Cognitive deficits include deficits on the Wisconsin Card Sorting Test, Mini-Mental State Examination, Graded Naming Test, Object Decision, Benton Judgment of Line Orientation, Paced Auditory Serial Addition Test, Sentence Completion Test, Story Recall, Stroop Test, Spoken Verbal Fluency Test, Raven Progressive Matrices and various WAIS-R subtests including Similarities and

Backwards Digit Span (Abrahams et al., 2005; Moretti et al., 2002; Neary, Snowden, & Mann, 2000). Some studies also report poor memory performance on tasks involving free recall (Neary et al., 2000), though findings of memory deficits are not as common as findings of cognitive deficits. It should be noted that these findings have not been consistently replicated in all studies of cognitive change in ALS and that these changes tend to occur only in a minority of individuals.

Though several studies of ALS have shown DLPFC involvement, the role of the OFC has not been investigated in this group, but has been shown to be involved in MND dementia. OFC damage can result in overt behaviour change with apparent sparing of function on standard tests of executive function (Bechara et al., 2000; Stone et al., 1998). Although it may initially appear that executive functions are intact in these individuals, several more experimental measures have been developed which are particularly sensitive to dysfunction of the OFC. Punishment/reward contingency learning paradigms have revealed perseveration deficits possibly linked to an insensitivity to future consequences in individuals with damage to the OFC and ventro-medial pre-frontal cortex (VMPFC) (Bechara, Damasio, Damasio, & Anderson, 1994; Bechara, Tranel & Damasio, 2000; O'Doherty, Kringelbach, Rolls, Hornak & Andrews, 2001; Rolls et al., 1994). These tasks include the Iowa Gambling Task (IOGT) (Bechara et al., 1994; Bechara et al., 2000) and a task which involves selecting between two visual stimuli resulting in hypothetical monetary gain or loss (O'Doherty et al., 2001; Rolls et al., 1994). Furthermore, individuals with selective damage to the OFC and individuals with FTD have been shown to be impaired on a high order Theory of Mind (ToM) task, the "Faux Pas Test" (Gregory et al., 2002; Stone & Baron-Cohen, 2002; Stone, Baron-Cohen & Knight, 1998). These tasks may be of use in identifying the subtle cognitive changes seen in some individuals with ALS who do not also exhibit FTD.

Graded Naming Test

The Graded Naming Tests (GNT), a measure of confrontation naming ability, involves naming a series of 30 pictures which have a decreasing frequency of occurrence in the English language. Previous research has shown patients with ALS to be impaired on this measure compared to control participants in both cross sectional (Abrahams et al. 2004; Strong et al*.,* 1999) and longitudinal studies (Abrahams et al*.,* 2005).

Research findings related to measures involving the OFC

1 Iowa Gambling Task

Bechara et al. (1994) have developed and used a task known as the IOGT which can identify specific deficits relating to perseveration and punishment/reward learning. This task involves selecting cards, one at a time from one of four decks, resulting in feedback indicating hypothetical monetary gain or loss. Various adaptations have been used with differing reinforcement schedules and patterns of responses but the general principle of the task is as follows: two decks will give high immediate reward but even higher delayed punishment, these two are the bad decks and result in overall monetary loss. The other two decks will give low immediate reward but also low delayed punishment leading to overall monetary gain, these are the good decks (Bechara et al., 1994; Bechara et al., 2000). The task has been designed so that participants are uncertain of the results from each deck and uncertain of the outcome that they will receive on picking a card (Bechara et al., 1994). Before starting the task, participants are told that "Out of these four decks of cards, there are some that are worse than others, and to win you should try to stay away from bad decks. No matter how much you find yourself losing, you can still win the game if you avoid the worst decks." Given this information, participants then have to learn which are the bad decks and try to avoid them (Bechara et al. 2002). In spite of this hint, Bechara et al. (1994) found that when asked, participants failed to identify accurately the frequency of gains or losses associated with each deck. Consequently, the IOGT is thought to test the ability to gauge or estimate which decks are going to be better in a way that is similar to

decisions regarding behaviour in social situations. Maia and McClelland (2004) have recently questioned this assumption, suggesting that participants have more conscious knowledge than previously thought, although it should be noted that Maia and McClelland's study was only assessing normal individuals who showed no cognitive changes.

Initially the IOGT was used with individuals who had damage to the VMPFC. These individuals showed insensitivity to the consequences of their actions and therefore impairments on the IOGT, but showed spared intellectual and problem solving abilities (Bechara et al., 1994). Their study actively discriminated for these individuals because they exhibited abnormal and detrimental decision making behaviour. They found that individuals with VMPFC damage picked significantly more cards from bad decks compared with control participants who picked more cards from good decks. Bechara et al. (1994) proposed three possible explanations for this: hypersensitivity to reward, insensitivity to punishment or insensitivity to future consequences resulting in a focus on current benefits.

The basis for deficits on the IOGT observed in individuals with frontal dysfunction has been further explored by Bechara et al. (2000) using a similar group with VMPFC damage. Their study concluded that the most probable explanation for poor performance on the IOGT in this group is an insensitivity to future consequences. The somatic marker hypothesis (Damasio, 1994, as cited in Bechara et al., 2000) is thought to provide the best explanation of these findings by Bechara and his colleagues (Bechara et al., 1994; Bechara et al., 2000), though some researchers question this assumption (Maia & McClelland, 2004; Maia & McClelland, 2005). Bechara et al. (1994) propose that individuals with VMPFC damage can identify what the consequences of an action may be but are then unable to act on it. They suggest that these individuals have stable representations of possible future consequences but these representations are not somatically tagged as either positive or negative outcomes (Bechara et al., 1994; Damasio, 1994, as cited in Bechara et al., 2000). Therefore, these individuals find it difficult to decide whether future

consequences should be aimed for or avoided. Bechara et al. (2000) showed that modifications to the IOGT which increased the punishment received in later selections for bad decks and decreased the reward received in later selections for good decks did not change the behaviour of their participants so that they were more likely to select good decks. They claim that this shows that such individuals are not hypersensitive to reward or insensitive to punishment, therefore insensitivity to future consequences or "myopia for the future," as explained by the somatic marker hypothesis, has been posited as the most likely explanation (Bechara et al., 2000, p. 2198).

2 Visual Discrimination Learning Task

Another punishment/reward contingency learning paradigm, similar to the IOGT has been used with individuals with damage to the OFC (O'Doherty et al., 2001; Rolls et al., 1994). This task is referred to as the Visual Discrimination Learning Task (VDLT). Rolls et al. (1994) tested individuals with damage to the OFC with a task of visual discrimination in which one image was linked to reward and the other a lack of reward or punishment. This task was designed to assess the speed of response to reversal of the learned reinforcement associations. They presented one of two different fractal patterns to their participants on a computer screen one at a time. Their participants were rewarded with a point for touching the correct pattern or for not touching the incorrect pattern and punished by loosing a point for touching the incorrect pattern. Feedback was given after each selection as to whether the selection was correct or incorrect (Rolls et al., 1994). Reinforcement contingencies were then swapped between the two patterns once nine out of 10 correct responses was achieved.

On switching reinforcement contingencies, Rolls et al. (1994) found that individuals with OFC damage showed perseveration. These individuals were shown to be aware of the rule change from a subsequent interview but appeared unable to disengage at the time. They noted that controls found it significantly easier to accommodate to reversed contingencies than individuals with

ventral frontal lobe damage. They suggest that this learning deficit may be related to emotional learning of when a behaviour should be stopped or in what context rules need to be switched when a behaviour becomes inappropriate. A proposed mechanism is that the OFC receives visual and auditory information which is then processed in the form of rapidly learning and relearning associations attached to these inputs in relation to punishment or reinforcement, and that these contingencies are remembered for use in similar future situations (Rolls et al., 1994).

O'Doherty et al. (2001) employed a similar reversal learning task to investigate OFC activation in a functional Magnetic Resonance Imaging (fMRI) study. This task involved selecting between two fractal pictures that appeared one above the other on a computer screen, resulting in either hypothetical financial gain or hypothetical financial loss. Both pictures could give either rewards or punishments but the relative magnitudes of the reward/punishment contingencies were such that one picture was more advantageous than the other. O'Doherty et al. (2001) claim that reversal of behavioural responses after a change in reward/punishment contingencies may be associated with a representation of these learnt contingencies in the OFC. They also suggest that the OFC may be involved in switching between reward/punishment contingencies, or relearning learning new contingencies. fMRI has shown medial and lateral OFC activation during rewarding and punishing selections when compared to a control condition of the same task in which neutral feedback was given (O'Doherty et al., 2001). Within the OFC, medial areas were active during a punishing response and lateral areas during a rewarding response. The magnitude of this activation increased with the magnitude of financial gain or loss. They propose that this differential activation of the OFC may also account for some of the deficits exhibited on tasks such as the IOGT by individuals with similar patterns of frontal lobe damage.

3 Faux Pas Test

The OFC also appears to be involved in social cognition processes. Patients with damage to the OFC have been shown to be impaired on the Faux Pas Test, which is a high level Theory of Mind

task involving judgments about social situations. This test is normally passed by children at between nine and 11 years old (Baron-Cohen, O'Riordan, Stone, Jones, & Plaisted, 1999; Gregory et al., 2002; Stone et al., 1998). A faux pas occurs when someone says something they should not have said but does not realise or know that they should not have said it (Gregory et al., 2002; Stone et al., 1998). In order to understand that a faux pas has occurred, two or more representations of mental states need to be compared. Firstly, there needs to be an understanding that the individual committing the faux pas, that is the individual who said or did something offensive, does not realise that their actions or words are offensive. Secondly, there needs to be an understanding that the recipient of the faux pas would feel an unpleasant emotion as a result of the other's actions (Gregory et al., 2002; Stone et al., 1998). The Faux Pas Test involves reading a series of short stories that are about a paragraph long, each containing a faux pas. The participant is read each story, also having a copy of it to follow along and refer back to in order to reduce demands on working memory. A set of questions are then asked to determine whether the participant can identify the faux pas, to determine whether the participant can empathise with the recipient and two control questions are asked to check that the participant has understood the story (Gregory et al., 2002; Stone et al., 1998; Stone & Baron-Cohen, 2002). Stone et al. (1998) employed a version of the Faux Pas Test with 10 stories, all of which contained a faux pas, however more recent studies have used a version which also included 10 control stories which contain a small conflict but not a faux pas (Gregory et al., 2002; Stone & Baron-Cohen, 2002).

This type of task has traditionally been used with autistic individuals with Asperger's syndrome; these individuals show an understanding of the story, but fail to identify the faux pas (Baron-Cohen et al., 1999; Stone et al., 1998). A deficit on this type of task may have a similar neurological basis to that seen in those individuals with frontal damage who show an insensitivity to future consequences on punishment/reward contingency learning paradigms. Stone et al. (1998) found that individuals with bilateral lesions to the OFC performed in a similar manner to individuals with Asperger's syndrome on the faux pas related question and were significantly

impaired in their performance on this task in comparison to control participants. However, they performed normally on control questions, indicating that they understood the story and performed normally on the question regarding empathy. Stone et al. (1998) noted that an inability to answer the question "why shouldn't he/she have said it or why was it awkward", as shown by some of their OFC patients, indicates that recognition of a faux pas requires an understanding of the effect of an individual's actions and words on others, not merely the ability to assign mental states to others. A proposed explanation for these findings is that those with damage to the OFC have difficulty linking emotional understanding with Theory of Mind inferences (Stone et al., 1998). This explanation supports the hypothesis that the OFC and amygdala are involved in interpreting the impact of other people's actions in ToM tasks (Brothers & Ring, 1992, as cited in Stone et al., 1998). Patients with FTD have also shown similar deficits on the Faux Pas Test (Gregory et al., 2002; Stone et al., 1998). These researchers found that the degree of ventromedial frontal atrophy in participants, showed an association with performance on the Faux Pas Test; greater atrophy resulted in poorer performance. They suggest that this is evidence of frontal involvement in understanding ToM tasks, particularly involvement of the ventromedial cortex. Stone et al. (1998) and Gregory et al. (2002) propose that the OFC is part of a circuit of ToM and not an area of localisation.

Aims of this study

This study shall focus on exploring the existence of cognitive changes in ALS non dementia patients that have been seen to be concomitant with subtle behavioural changes such as impulsiveness and emotional changes. It will not discuss the area of behaviour change in ALS. This study seeks to investigate further the prevalence and variety of cognitive changes observed in patients with ALS on dementia by assessing a group of patients with ALS non dementia in comparison to a control group of normal individuals matched for age, years of full time education and estimated Full scale IQ. Assessment will involve tests of executive functioning including the WVFI, the IOGT, a VDLT similar to the one used by O'Doherty et al. (2001), the Faux Pas Test

and the Graded Naming Test. These tests were used in order to ascertain if deficits observed in individuals with orbitofrontal damage, are also present in a section of individuals with ALS non dementia.

Hypotheses

As cognitive changes are only thought to occur in 25 to 50 percent of individuals with ALS non dementia, our hypotheses are that some of the individuals with ALS will show poorer performance on the WVFI and GNT in comparison to control participants as has been previously demonstrated (Abrahams et al., 2005; Abrahams et al. 2004; Strong et al., 1999). We suggest that some individuals with ALS will make more selections from bad decks and fewer selections from good decks on the IOGT and fail to respond quickly to changed contingencies in the VDLT in comparison to control participants. We suggest that some individuals with ALS may also perform worse than control participants on some of the specific faux pas questions on stories containing a faux pas in the Faux Pas Test, but that there will be no difference between individuals with ALS and control participants on the control questions, empathy question and on the questions for the control stories. We also suggest that ALS patients will perform worse than controls on the GNT.

Method

Selection of Participants

ALS patients

Patients with ALS were recruited through the regional MND service at the Western General Hospital, Edinburgh. Inclusion criteria for ALS patients were as follows: aged between 30 and 80, first language English (an understanding of English is necessary for some of the tests of cognitive function) and evidence of both lower motor neurone and upper motor neurone degeneration in one or more regions, in accordance with criteria in Brooks et al. (1998). Patients with severe disability were excluded as they would find the interview and testing period of

approximately two hours excessively physically taxing. Information regarding suitability was obtained from patients' records held at the Western General Hospital prior to inviting patients to participate and ethical approval was gained from the NHS Lothian regional ethics committee. A total of 34 individuals with ALS were contacted and invited to participate, 20 of these responded and agreed to participate, two responded and declined to participate and 12 did not respond at all. This gives a response rate of 65%. Of the 20 who agreed to participate only 10 were able to be tested for the purpose of this study due to time constraints. Of the 10 who took part there were five male and five female participants and all were right handed. Nine of these were sporadic cases with no reason to suspect a familial involvement and in one case there was a family history of MND but no definitive familial diagnosis had been made. All patients were interviewed in their own home at a time of day convenient to them.

Control participants

Ten healthy control participants were also recruited: five male, five female and all right handed. These were chosen to be appropriately matched to the patient group for age and years of full time education. All control participants also had English as their first language. These participants were recruited from the experimenters' friends and family. None of the control participants had sustained a significant head injury and none had a history of neurological disorder. Controls were interviewed either in their own homes or at the Psychology Department at the University of Edinburgh at their convenience. Financial compensation for travel expenses was offered to control participants.

Experimental measures and procedure

The following procedure was approved by the NHS Lothian regional ethics committee and the ethics committee at the Psychology Department of the University of Edinburgh.

Interview procedure

All participants took part in a session of interviewing and testing which lasted approximately two hours. When participants were initially contacted a brief summary of the study was provided. Prior to beginning the period of interviewing and testing, participants were given the opportunity to read a more detailed information sheet outlining the aims of the study as required by ethical guidelines. All participants were informed that their participation was voluntary and that they had the right to withdraw at any time. They were also asked to sign a consent form (see appendix 1). Demographic information was then recorded, consisting of age, gender, handedness, years in full time education, occupation and questions about medical history in accordance with the exclusion criteria mentioned above. In addition, patients with ALS were asked about when they first noticed their symptoms, the region of onset e.g. limbs or bulbar, their date of diagnosis and time since diagnosis. During this preliminary interview with patients, the ALS functional rating scale was completed (Brooks et al., 1996). The remainder of the interview consisted of two parts, a series of cognitive tests lasting approximately one hour and 25 minutes, followed by a series of behavioural tests and questionnaires which formed part of a separate study and shall not be discussed further (see project by Alan Dunlop). The order of the cognitive tests was as follows: National Adult Reading Test, second edition (NART) (Nelson & Willison, 1991), WVFI generation conditions (Abrahams et al*.,* 2000), IOGT (Bechara, 2002), the Faux Pas Test (Stone & Baron-Cohen., 2002), a computer based VDLT based on that developed by O'Doherty et al. (2001), WVFI control condition (Abrahams et al*.,* 2000) ending with the Graded Naming Test (McKenna & Warrington, 1983). For the NART and the Faux Pas Test participants gave permission for their voice to be recorded to aid subsequent analysis and to speed up the interview process. All voice recordings used the following equipment: a Sony ECM-Z60 microphone in conjunction with a Griffin iMic USB Audio Interface. This was connected to an 800mhz Apple ibook running Mac OS X 10.4.4 operating system and Final Vinyl 1.1.2 audio recording software.

Background measure, the National Adult Reading Test

The NART (Nelson & Willison, 1991) was administered and scored in accordance with the standard procedure as described in the instruction manual. This measure was recorded so that the patient and control groups could be matched on estimated full scale IQ. Derivation of this full scale IQ estimate from the NART error score is described in the approach to analysis section. The NART is thought to provide a pre-morbid IQ estimate for patients and an estimate of current IQ for controls.

Experimental measures

Written verbal fluency index

The WVFI was administered as described in Abrahams et al. (2000 p.736). In summary, this task involved two generation conditions, the first was writing down as many words beginning with the letter "S" in five minutes as the participant could think of, the second, writing down as many four letter words beginning with "C" as the participant can think of in four minutes. There was a later control condition designed to factor out the effect of writing speed. This involved timing the participant as they copied out their previously generated lists. In addition to the information regarding the WVFI given in Abrahams et al. (2000), participants were instructed to write their lists of words on a pad of lined paper in a vertical column, one word on each line. In the control condition they were asked to copy their original list as quickly as possible on the same piece of paper. It was then possible to calculate a WVFI for the two generation conditions and an overall WVFI across both generation conditions as described in Abrahams et al. (1997 p.465) and Abrahams et al. (2000 p.736). Generation times and copy times are all measured in seconds.

Iowa Gambling Task

Participants were asked to play a computer game, which was a computerised version of the original ABCD variant Iowa Gambling Task (Version 2.0 2002). See Bechara et al. (2000 p.2194) for details of this task. The task was presented on a PC laptop computer with a 14 inch

screen at a resolution of 1024x768 pixels running Windows ME operating system. Participants used either a Logitech Cordless Notebook Mouse or the laptops' built in track pad device to select card decks. The computerised task differed from the original IOGT in that bad decks would give greater delayed financial punishments and good decks greater delayed financial rewards in comparison to immediate financial reward received (Bechara et al., 2000). (For details of the punishment reward schedule used, see Table 1). The computerised IOGT lasted for a duration of 100 trials, a trial involves making one selection of a card from a deck. The instructions used for this task are shown below. In this task instructions were read aloud to the participants who also had their own a copy for reference. The configurable parameters for this computer task were set to the default values, apart from the inter-trial interval which was set to the recommended 500 milliseconds, as no physiological measurements were being recorded.

Iowa Gambling Task - Instructions

1. In front of you on the screen, there are 4 decks of cards: A, B, C, and D.
2. When we begin the game, I want you to select one card at a time by clicking on a card from any deck you choose.
3. Each time you select a card, the computer will tell you that you won some money. I don't know how much money you will win. You will find out as we go along. Every time you win, the green bar gets bigger.
4. Every so often, when you click on a card, the computer will tell you that you won some money as usual, but then it will say that you lost some money as well. I don't know when you will lose or how much. You will find out as we go along. Every time you lose, the green bar gets smaller.
5. You are absolutely free to switch from one deck to the other at any time, and as often as you wish.
6. The goal of the game is to win as much money as possible and avoid losing as much money as possible.
7. You won't know when the game will end. Simply keep on playing until the computer stops.

8. I am going to give you $2000 of credit, the green bar, to start the game. The red bar is a reminder of how much money you borrowed to play the game, and how much money you have to pay back before we see whether you won or lost.
9. The only hint I can give you, and the most important thing to note is this: Out of these four decks of cards, there are some that are worse than others, and to win you should try to stay away from bad decks. No matter how much you find yourself losing, you can still win the game if you avoid the worst decks.
10. Also note that the computer does not change the order of the cards once the game begins. It does not make you lose at random, or make you lose money based on the last card you picked.
11. We are not able to pay you any actual money at the end of the game, but please try to win as much as you can during the game, have fun!

Table 1: Reinforcement schedule used in the IOGT

Selection number	Deck A		Deck B		Deck C		Deck D	
	Win	Lose	Win	Lose	Win	Lose	Win	Lose
1	100	0	100	0	50	0	50	0
2	120	0	80	0	60	0	40	0
3	80	150	110	0	40	50	45	0
4	90	0	120	0	55	0	45	0
5	110	300	90	0	55	50	55	0
6	100	0	100	0	45	0	60	0
7	80	200	90	0	50	50	40	0
8	120	0	120	0	45	0	55	0
9	110	250	110	1250	60	50	50	0
10	90	350	80	0	40	50	60	250
11	110	0	110	0	55	0	55	0
12	130	350	100	0	55	25	40	0
13	90	0	90	0	65	75	60	0
14	100	250	130	1500	45	0	40	0
15	120	200	120	0	70	25	45	0
16	110	0	130	0	40	0	55	0
17	90	350	110	0	50	25	65	0
18	130	150	90	0	60	75	70	0
19	120	250	100	0	70	0	50	0
20	100	0	120	0	40	50	70	275
21	120	250	120	1750	60	0	60	0
22	140	300	110	0	65	25	55	0
23	110	0	140	0	55	0	65	0
24	110	350	130	0	80	50	80	0
25	100	0	100	0	40	25	40	0
26	120	200	110	0	60	50	80	0
27	130	250	120	0	55	0	40	0
28	110	150	120	0	65	25	65	0
29	140	250	140	0	40	75	55	300
30	120	0	110	0	80	50	60	0
31	130	350	130	0	65	25	65	0
32	120	200	140	2000	75	0	75	0
33	140	250	120	0	55	25	60	0
34	130	250	110	0	60	25	65	0

35	110	150	130	0	70	25	75	325
36	150	0	150	0	65	0	85	0
37	140	150	110	0	55	75	45	0
38	120	300	150	0	75	25	55	0
39	150	350	120	0	45	50	70	0
40	110	0	140	0	85	75	55	0
41	140	350	140	0	70	25	70	0
42	130	200	150	0	80	0	80	0
43	150	250	130	0	60	25	65	0
44	140	250	120	0	65	25	70	0
45	120	100	140	0	75	25	80	350
46	160	0	160	2250	70	25	90	0
47	150	150	120	0	60	75	50	0
48	130	300	160	0	80	25	60	0
49	160	350	130	0	50	50	75	0
50	120	250	150	0	90	75	60	0
51	150	350	150	0	75	25	75	0
52	140	200	160	0	85	25	85	0
53	160	250	140	0	65	25	70	0
54	150	250	130	0	70	25	75	0
55	130	150	150	0	80	25	85	0
56	170	250	170	0	75	25	95	0
57	160	150	130	0	65	75	55	0
58	140	300	170	2500	85	25	65	375
59	170	350	140	0	55	50	80	0
60	130	250	160	0	90	75	65	0

Table 2: Reward/punishment ratios and ranges for the VDLT,

reproduced from O'Doherty et al. (2001 p.96)

	Rewarding stimulus	Punishing stimulus
Reward / punishment ratio	70:30	40:60
Reward ranges	£80–250	£30–60
Punishment ranges	£-10 to -60	£-250 to -600

Visual Discrimination Learning Task

This task was based on that described in O'Doherty et al. (2001) and was designed using Visual Basic Version 6.0 for 32bit Windows development running under Microsoft Windows 98 Second Edition, using the basic Visual Basic toolkit for with no additional control types. In this task, participants received hypothetical financial gain or loss after selecting one of two easily distinguishable fractal patterns presented one above the other on a computer screen. (See appendix 2 for the stimulus fractal patterns). The computer and mouse used for this task was the same as the one used in the IOGT. The two fractals appeared on the computer screen one above the other, on a white background with the text “Choose one Picture” between them (see Figure

1). Before any selections were made, the computer program had designated one fractal pattern as the rewarding stimulus and the other as the punishing stimulus. The rewarding stimulus gave high rewards or low punishments in the form of hypothetical financial reward or loss, the punishing stimulus giving low rewards and high punishments. The possible ranges of hypothetical financial loss or gain for both the rewarding and punishing stimuli were the same as those used by O'Doherty et al. (2001 p.96) (see Table 2). The participant's task was to determine by trial and error which of the fractal patterns was the punishing stimulus and which was the rewarding stimulus. After a participant had correctly selected the rewarding stimulus in nine out of 10 consecutive selections the punishment/reward contingencies of the two fractal patterns were swapped so that the previous rewarding stimulus became the punishing stimulus and vice versa. This is known as "reaching criterion". The participant's task was to realise that this had happened and switch to selecting the new rewarding stimulus. Participants were not explicitly informed that this is what they had to do but were instead given a more general set of instructions, these instructions are listed below.

The computer program recorded the fractal selected for each trial, and whether the selection was of the rewarding stimulus or the punishing stimulus. It also recorded which fractal picture was the initial rewarding stimulus and recorded every time criterion was reached. From the results recorded by the computer program, the following variables were created: total number of times criterion reached (max. 4), number of trials to the first time criterion reached (min. 9), number of errors to the first criterion, number of trials between first and second criterion (min. 9), number of errors between first and second criterion, number of the last error trial before the second criterion, number of trials after the first criterion and number of errors after the first criterion. Participants continued to make selections between the fractal patterns until they had performed 100 trials, or until they had reached criterion four times. On selecting a picture, the previous image of the two fractals and the text "Choose one Picture" was replaced by either a cartoon of a yellow smiley face in the centre of the screen above the text "Well done – you have won £xxx", or a similar

cartoon of a blue sad face above the text “I’m sorry – you have lost £xxx”, where xxx is the hypothetical amount won or lost. Money could be won or lost when selecting either the punishing or rewarding stimulus. After making an initial selection the total amount won or lost was displayed to the right of the fractal patterns as the amount written in figures along with a stack of coins (see Figure 1). If the participant was winning overall, this was displayed in green and if loosing, in red. This feedback remained on the screen for the remainder of the game and was updated after each selection. After each selection, the fractals were removed and immediately replaced with the cartoon face and corresponding message which remained on the screen for a total of three seconds. After the cartoon face was removed, the screen was white apart from the summary of the amount won or lost on the right hand side. There was a period of one second between the removal of the cartoon face and the reappearance of the two fractal patterns. When the fractal patterns reappeared, their positions, e.g. upper fractal pattern or lower fractal pattern, were determined at random. The rewarding and punishing contingencies associated with each fractal image stayed the same until criterion was reached, irrespective of whether the fractal pattern appeared in the upper or lower position in the screen.

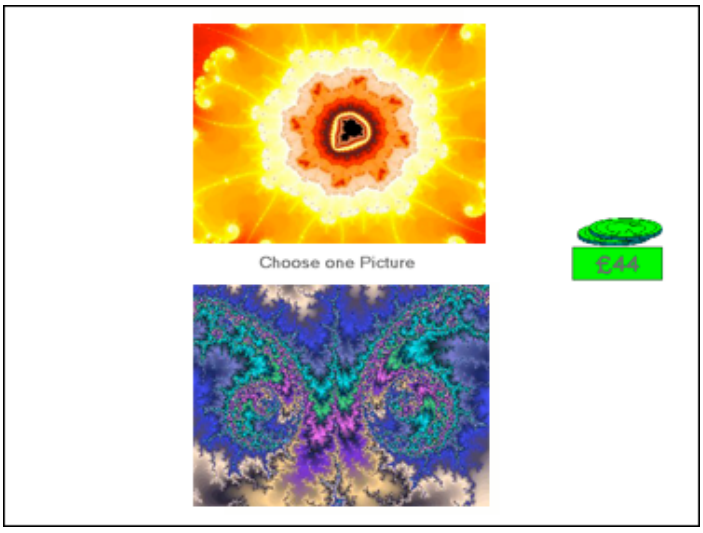

Figure 1

Visual Discrimination Learning Task - Instructions

Participants were given the following instructions prior to starting this task, these were read aloud to the participants who also had their own copy for reference.

12. In front of you on the screen, there are two pictures, one above the other.
13. When we begin the game, I want you to select a picture by clicking on it. If this is difficult for you, just point to the picture and I will select it for you.
14. Each time you select a picture, the computer will tell you that you have won some money, or that you have lost some money. I don't know how much money you will win or lose. You will find out as we go along.
15. The amount of money you have won or lost is displayed to the right of the pictures as a pile of coins and the amount written in pounds. If you are winning overall, the coins and the amount are in green, and if you are loosing, red.
16. The pictures will always stay the same but sometimes they will swap positions.
17. You will see that sometimes one picture will be better than another at winning money. It doesn't matter which position it is in. You are absolutely free to switch from one picture to the other at any time, and as often as you wish.
18. The goal of the game is to win as much money as possible and avoid losing as much money as possible.
19. We are not able to pay you any actual money at the end of the game, but please try to win as much as you can during the game , have fun!

The Faux Pas Test

The Faux Pas Test involved presenting a series of short stories to participants. The experimenter said, "I'm going to be reading you some brief stories and asking you some questions about it. You have a copy of the story in front of you so you can read along and go back to it." Then the experimenter read aloud the stories, which the participants could follow along with their own typed copy. Half of these stories contained a faux pas, "faux pas stories", and half did not,

“control stories”. After reading each story, participants were asked several questions to assess their understanding of the story. These questions were either “faux pas questions”, which assessed understanding of whether a faux pas had been committed, or “control questions” which checked whether the participant had understood and remembered the content of the story. All stories and questions are listed in appendix 3. The first faux pas question was “Did anyone say something they shouldn’t have said or something awkward?”. If participants answered ‘no’ to this question, the two control questions were then asked. If they answered ‘yes’, five more faux pas questions were asked: Who said something they shouldn't have said or something awkward?, Why shouldn't he/she have said it or why was it awkward?, "Why did they say it?" or "Why do you think they said it?", “Did X know that Y?” and “How did X feel?”. After the faux pas question/questions, two control questions were asked. For control stories, participants were expected to answer ‘no’ to the first faux pas question. For faux pas stories participants were expected to answer ‘yes’ to the first faux pas question and to give appropriate answers to the rest of the faux pas questions. The rationale behind what each of these questions is assessing and a detailed description of how to score them is given in Stone and Baron-Cohen (2002).

The Faux Pas Test was administered as described in Stone and Baron-Cohen (2002) with the following alterations: story 11, a faux pas story, was removed because it contained a reference to a joke about a terminal illness. It was thought that this could be upsetting for the patients in our study. As this faux pas question was removed, control question 20 was chosen to be removed at random. For the purpose of administering the Faux Pas Test, the stories were re-numbered from one to 18, however any reference made to specific faux pas stories in this study shall refer to the original story number as indicated in Stone and Baron-Cohen (2002). Additionally, US English spellings and vocabulary used in Stone and Baron-Cohen (2002), were changed to British English, e.g. changing the phrase “elementary school” for “primary school”. See appendix 3 for a copy of the faux pas stories used with all changes. There were no other deviations from the procedures set out in Stone and Baron-Cohen (2002).

Graded Naming test

The Graded Naming test (McKenna & Warrington, 1983) was given to all participants. This test involved showing participants a booklet of 30 pictures of increasing difficulty and asking "What is this?". Cues could be given in the form of pointing, perceptual reorientation and semantic reorientation. The Graded Naming Test was administered and scored in accordance with guidelines given in McKenna and Warrington (1983).

Statistical design

The analyses consisted of a comparison between patients and the control group on each separate variable in each of the cognitive tests, except for the IOGT. These simple comparisons consisted of *t* tests for variables which showed a normal distribution and Mann-Whitney U tests for variables which did not fit a normal distribution. No attempt was made to correct for the possibility of inflated Type One error caused by the large number of separate comparisons and this should be taken into consideration when looking at the results. It was felt that an overly conservative analysis would be detrimental, as the goal of this study was to investigate suitable areas of investigation and suitable directions for future research to follow. The distribution of the data on each variable was assessed by examining a histogram.

All statistical procedures were applied to the raw score for that variable unless otherwise indicated. Scatter plots for variables with a non normal distribution indicated that on these variables the two groups were relatively homogeneous. Transformations which were applied to raw scores on selected variables were as follows:

1

NART error scores were used to calculate an estimated WAIS-R full scale IQ using the formula described in Nelson and Willison (1991 p.16).

2

For the IOGT the deck selections were broken down into five blocks; 1 (deck selections 1-20), 2 (deck selections 21-40), 3 (deck selections 41-60), 4 (deck selections 61-80) and 5 (deck selections 81-100). The scores for selections on decks A and B were combined to give a total score for selections of bad decks on each block and the scores for selections on deck C and D to give a total for good deck selections on each block. The analysis for the IOGT consisted of a 2x5x2 Analysis of Variance (ANOVA) comparing the between subjects variable of group, patients versus controls, with the within subjects variables of deck, good decks or bad decks, and block, card selection blocks 1-5.

3

For the Faux Pas Test the number of correctly identified faux pas stories and the number of correctly identified control stories were transformed to represent a percentage of the total number of stories after taking account of stories discarded for incorrect answers to control questions.

A percentile analysis was conducted for each variable on each of the experimental measures. This involved comparing the scores of individual patients to the scores of the control group to ascertain whether any patients fell below the 2.5^{th} percentile or above the 97.5^{th} percentile of the distribution of scores from the control group implying whether any individual patient's score on any variable fall above or below ± 1.96 standard deviations from the mean of the control group for that variable.

Results

Demographic information and background measures

The patient and control groups were well matched for age, number of years in full time education and on an estimate of WAIS-R Full scale IQ derived from the NART. Two patients were not able

to complete the NART due to dysarthria. Mann-Whitney U tests and *t* tests found no significant differences between patient and control groups on any of the demographic or background variables (see Table 3). Background information for the patient group is also reported in Table 4, showing the progression and severity of ALS represented in our sample. Table 5 shows a summary of the occupational history of both patients and controls.

Table 3: Summary of background measures for patient and control groups

Mean ± SD (range, min-max) along with *t U* and *p* values

	ALS patients	Controls	*t* value	*U* statistic [a]	*p* value
Age	62.50 ± 10.94 (31-78)	56.20 ± 10.95	-1.079	-	≥0.05
Years in full time education	12.60 ± 4.12 (7-20)	14.75 ± 4.16 (10-21)	-	36.00	≥0.05
WAIS-R Full scale IQ estimate from NART	114.17 ± 10.41 (100-128)[b]	107.16 ± 14.22 (87-124)	-	27.50	≥0.05

[a] U statistic from Mann-Whitney U analysis.

[b] n=8 for ALS patients IQ estimate. n=10 for all other entries in this table.

Table 4: Additional background measures recorded for the patient group.

	Mean ± SD (range, min-max)	Number of patients with onset in a particular region
Time since onset in (years)	5.50 ± 4.17 (2-16)	-
Time since diagnosis (months)	27.56 ± 24.55 (6-84)	-
ALS Functional Rating Scale score	29.90 ± 11.94 (14-47)	-
Region of symptom onset	-	0 Bulbar 4 Lower limbs 2 Upper limbs 4 All limbs

Table 5: Occupation of ALS patients and control participants.

Participants occupational category	No. of ALS patients in each category.	No. of controls in each category.
Managerial and professional	1	1
Lower managerial and professional	2	4

Intermediate occupation	1	2
Small employers	1	0
Lower supervisory and technical	0	0
Semi routine	2	0
Routine	2	0
Never worked or long term unemployed	0	3
Unknown	1	0

Cognitive Measures

Written verbal fluency index

The scores for patients and controls on all WVFI variables were comparable with the notable exception of one control (see Table 6). Control eight performed particularly poorly and he also had a low level of time spent in education, only ten years and a NART score of 87. Three *t* tests showed no significant differences between patient and control groups on the overall WVFI, or on either of the two sub conditions: words beginning with "S" and words beginning with "C" (see Table 6). Four patients did not complete the WFVI due to motor difficulties. A percentile analysis showed that none of the patients' scores fell below the bottom 2.5th percentile for the distribution of scores for control participants on any of the WVFI variables.

Table 6: Analysis of Written Verbal Fluency Index.

Mean ± SD (range, min-max) along with *t* and *p* values

	ALS patients	Controls	*t* value	*p* value
WVFI "S"	5.55 ± 2.85 (2.68-10.33)	6.58 ± 4.57 (2.75-18.14)	0.492	≥0.05
WVFI "C"	12.49 ± 7.71 (4.79-26.67)	16.34 ± 9.27 (5.77-37.50)	0.852	≥0.05
Overall WVFI	7.53 ± 3.05 (3.54-11.74)	9.32 ± 5.82 (3.98-23.95)	0.692	≥0.05

ALS patients n=6 Controls n=10

Iowa Gambling task

All differences between the patient and control groups for the number of selections from each card deck A-D were in the direction described in the experimental hypothesis, with patients selecting more bad decks than controls and fewer good decks than controls, except for selections from deck C. When decks are collapsed into two variables, good decks and bad decks, differences between the patient and control groups are in the expected direction for all blocks after block one (See Figures 6 and 7). Figures 2-5 show that patients selected more cards from bad decks A and B than controls for all blocks after block one and patients selected fewer cards from deck D than controls for all blocks after block one. However, for deck C patients picked more cards than controls for all blocks apart from block five (see Figures 2–5). There is no theoretical justification for expecting a difference in any direction for block one, as at the start of block one participants have no experience which could inform them of which decks are advantageous and which are disadvantageous.

Although selections from deck C were not in the expected direction, of the good decks, controls favoured selections from deck D over selections from deck C (see Figures 4 and 5). Table 1 (method section) shows the exact punishments and/or rewards received for each selection from each deck. Deck C can be seen to give more consistent but smaller punishments and deck D less consistent but slightly larger punishments. It appears that control participants preferred the contingency of deck D. An ANOVA was performed comparing group, patients versus controls, with deck, good decks or bad decks, and block, card selection blocks 1-5. This showed no main effects for group or block, but did show a significant effect of deck. This main effect was due to participants selecting more good decks than bad decks in blocks 3-5 and more bad decks than good decks in block one. There was no interaction of group with deck or group with block and no interaction between group, deck and block. A significant interaction was found between block and deck (see Table 7). The interaction between deck and block was due to participants selecting more good decks than bad decks in block one and vice versa for all subsequent decks. As no

group differences were significant no further post hoc tests were carried out.

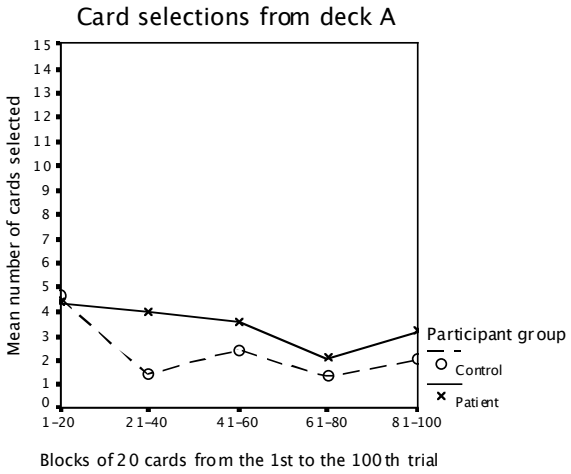

Figure 2

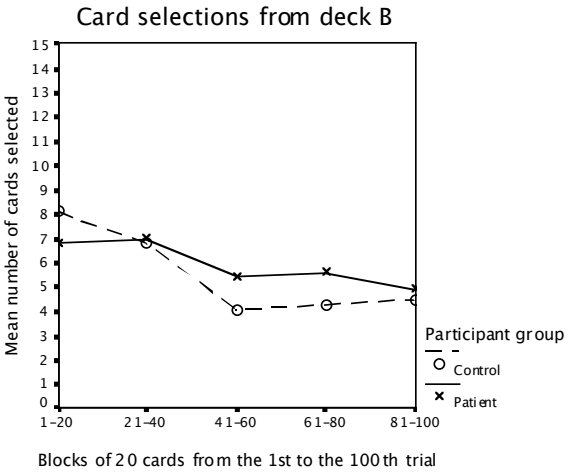

Figure 3

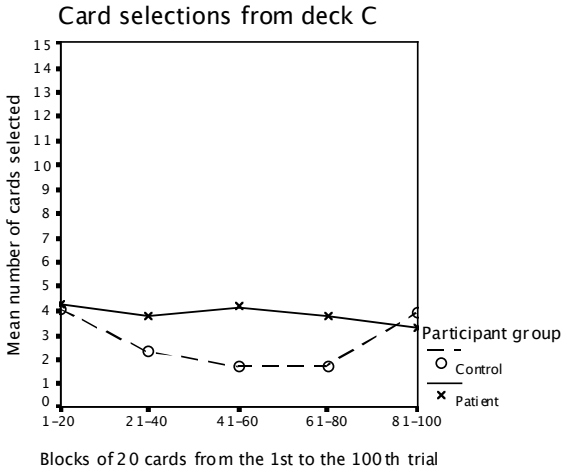

Figure 4

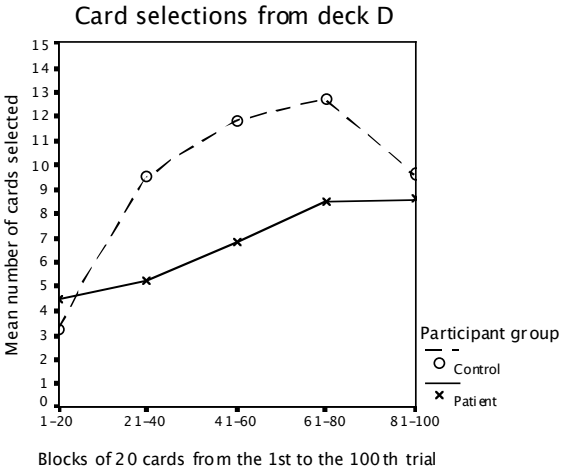

Figure 5

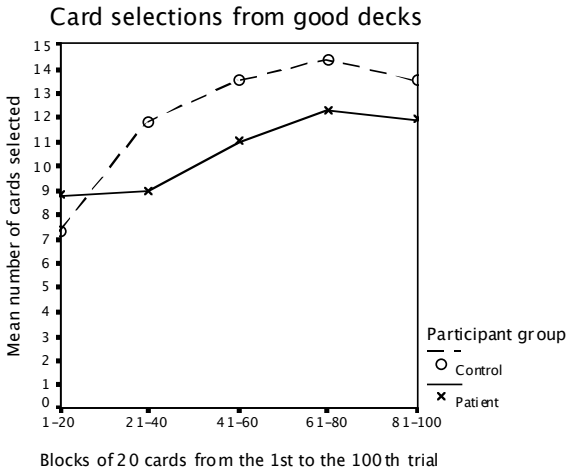

Figure 6

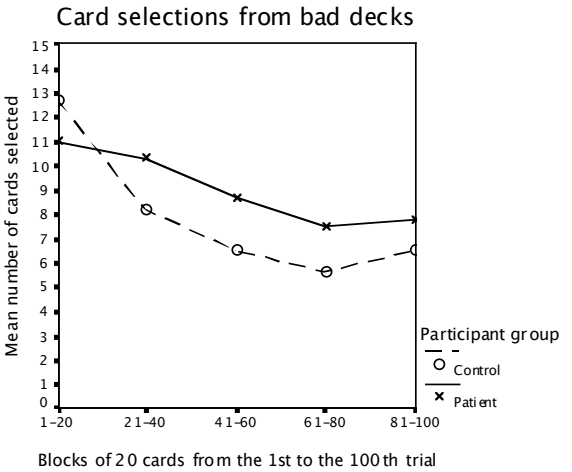

Figure 7

A percentile analysis comparing patients' scores to the distribution of control participants' scores on all IOGT variables showed that several patients were above the 97.5th percentile on bad deck variables. Also, several patients fell below the 2.5th percentile for good deck variables (see Table 8). Notably, patient 10 was outside the distribution of control participants on all variables apart from deck C selections. During testing this participant was the only one managed to select all the cards from a single deck, deck B, from which he selected the maximum of 60 cards.

Table 7: Results of an ANOVA analysis of the IOGT comparing deck, good decks or bad decks, and block, card selection blocks 1-5, with group, patients versus controls

Significant results are highlighted in **bold**.

	F	P value
Main effect of group	(1, 18) =1.000	≥0.05
Main effect of deck	**(1, 18) =5.798**	**<0.05**
Main effect of block	(4, 18) =1.000	≥0.05
Interaction group * deck	(4, 18) =1.245	≥0.05
Interaction group * block	(4, 18) =1.000	≥0.05
Interaction group * deck * block	(4, 18) =1.453	≥0.05
Interaction block * deck	**(4, 18) =9.358**	**<0.0001**

n=10 for the patient and the control group for all variables

Table 8: Percentile analysis and means table for the IOGT

Mean ± SD (range, min-max) along with the number of patients out with the normal distribution of control participants for each variable and the participant numbers of these patients.

	ALS patients	Controls	No of patients > ± 1.96 SD from control mean.	Patient numbers
Deck A[a]	17.30 ± 7.26 (8-30)	11.70 ± 4.03 (6-18)	5	4, 6, 8, 9, 10
Deck B[a]	29.70 ± 12.78 (16-60)	27.80 ± 8.47 (15-40)	1	10
Bad decks[a]	45.30 ± 18.64 (13-80)	39.50 ± 7.85 (25-50)	3	6, 9, 10
Deck C[b]	19.40 ± 6.77 (10-31)	13.70 ± 6.43 (5-24)	0	
Deck D[b]	33.60 ± 11.62 (10-49)	46.80 ± 9.20 (33-60)	3	2, 8, 10
Good Decks[b]	53.00 ± 15.94 (20-76)	60.50 ± 7.85 (50-75)	3	6, 9, 10

[a] These are patients at or above the 97.5th percentile who selected lots of bad decks.

[b] These are patients at or below the 2.5th percentile who selected very few good decks.

Visual Discrimination Learning Task

In this task patients took longer than controls to reach the first criterion and made more errors to the first criterion, consequently patients had fewer trials after the first criterion. The patient group made a similar number of errors to controls after the first criterion in spite of having fewer trials in which to make these errors (see Table 9). Two *t* tests showed a significant difference between patients and controls for the number of trials between the first and second criterion and the number of errors between the first and second criterion. The direction of this difference was contrary to the direction expected in our hypotheses, with controls taking more trials than patients and making more errors than patients between the first and second criterion (see Table 9). Mann-Whitney U tests and a *t* test showed no significant differences between the patient and control group for the total number of times criterion was reached, the number of trials to the first criterion, the number of errors to the first criterion, the number of the last error trial before the second criterion, the number of trials after the first criterion and the number of errors after the

first criterion (see Table 9). As one control and one patient did not reach criterion at all there were nine participants in each group for number of trials to the first time criterion reached, number of errors to the first criterion, number of trials after the first criterion and number of errors after the first criterion. As several participants did not reach criterion more than once, five patients were compared with six controls for number of trials between first and second criterion, number of errors between first and second criterion and number of the last error trial before the second criterion. Therefore results from these variables should be interpreted with caution.

A percentile analysis comparing patients' scores to the distribution of control participants' scores on all VDLT variables showed that several patients were above the 97.5th on variables where some patients might be expected to have higher scores due to perseveration. One patient, number 10, was below the 2.5th percentile for the control distribution for the number of the last error trial before the second criterion (see table 10). On questioning participants after the interview, none indicated that they had a conscious awareness that punishment/reward contingencies were switched between the two fractal patterns.

Table 9: Summary of analysis for the Visual Discrimination Learning Task

Mean ± SD (range, min-max) along with *t*, *U* and *p* values.

Significant results are highlighted in bold.

	ALS patients	Controls	*t* value	*U* stat[a]	*p* value
Total number of times criterion reached[a] (max 4)	1.90 ± 1.37 (0-4)	2.30 ± 1.49 (0-4)	-	42.500	≥0.05
Number of trials to the first time criterion reached[b] (min 9)	35.00 ± 31.75 (10-94)	18.67 ± 9.77 (9-38)	-	31.000	≥0.05
Number of errors to the first criterion[b]	15.33 ± 16.18 (1-48)	4.56 ± 4.04 (0-11)	-	28.500	≥0.05
Number of trials between first and	**15.80 ± 4.71 (10-23)**	**26.50 ± 5.75 (23-38)**	**3.324**	**-**	**<0.01**

second criterion[c] (min 9)					
Number of errors between first and second criterion[c]	**4.40 ± 2.41 (1-7)**	**11.17 ± 3.66 (7-16)**	**3.533**	**-**	**<0.01**
Number of the last error trial before the second criterion[c]	28.60 ± 15.47 (11-50)	33.50 ± 6.03 (27-42)	-	11.500	≥0.05
Number of trials after the first criterion[b]	56.67 ± 30.13 (6-90)	76.89 ± 13.72 (49-90)	-	23.500	≥0.05
Number of errors after the first criterion[b]	27.00 ± 17.10 (4-53)	34.78 ± 9.10 (19-49)	1.178	-	≥0.05

a N=10 patients N=10 controls

b N=9 patients N=9 controls

c N=5 patients N=6 controls

Table 10: Percentile analysis of the VDLT showing the number of patients who fell in the abnormal range compared with the normal distribution for control participants.

	No of patients > ± 1.96 SD from control mean.	Patient numbers
Total number of times criterion reached[a]	0	-
Number of trials to the first time criterion reached[a]	3	2, 8, 10
Number of errors to the first criterion[a]	4	2, 8, 9, 10
Number of trials between first and second criterion[a]	0	-
Number of errors between first and second criterion[a]	0	-
Number of the last error trial before the second criterion[a]	1	10
Number of trials after the first criterion[b]	3	2, 5[c], 8
Number of errors after the first criterion[a]	1	4

[a] These are patients at or above the 97.5th percentile.

[b] These are patients at or below the 2.5th percentile.

[c] Patient 5 had few trials after the first reversal as she was very good at the task and only took 43 trials to reach criterion 4 times, patients 2 and 8 took the full 100 trials. This patient was out with the normal range because she performed exceptionally well and therefore is not considered to show a deficit.

Faux pas test

The distribution of scores for the patients and control groups was relatively homogeneous for all variables on the Faux Pas Test (see Table 11), except for question four, the number of faux pas stories where participants correctly identified "Why do you think X said it?". For this variable, patient eight got none of these questions correct and patient 10 got only two of these questions correct. In response to question four, patient eight always indicated that he thought the comment was made intentionally, either to hurt or "to get one over" the other person in the story, or he said "I don't know". Patient 10 also gave atypical responses to question four and to other questions. During the Faux Pas Test, patient 10 spent a lot of time reiterating what the story said without actually answering the question, he often had to be prompted and asked the question again. During the interview it appeared that he was doing this because he was unsure of how he should answer the faux pas questions. These atypical responses are listed in Table 12 and the stories and questions for these responses are in appendix 3.

In spite of the atypical answers given by patients eight and 10, comparisons between the two groups using either *t* tests or Mann-Whitney U tests showed no significant differences for all variables. No faux pas stories were discarded for incorrectly answered control questions, however some control stories were discarded due to incorrect answers to control questions. Consequently, the scores for the number of correctly identified control stories were analysed as a percentage of the total number of correctly identified stories as suggested in accordance with scoring guidelines in Stone and Baron-Cohen (2002). The scores for the number of correctly identified faux pas stories were also analysed as a percentage rather than a raw score to aid comparisons between the

analysis of faux pas sorties and the analysis of control stories. A percentile analysis found that the same patients who gave atypical answers also fell at or below the 2.5th percentile of the distribution of scores for the control group for several variables (see Table 11).

Table 11: Means table and percentile analysis of the Faux Pas test

Mean ± SD (range, min-max) along with the number of patients out with the normal distribution of control participants for each variable and the participant numbers of these patients.

	ALS patients	Controls	No of patients > -1.96 SD from control mean.	Patient numbers
Score for faux pas related questions on faux pas stories (max 54)	47.30 ± 6.58 (38-54)	46.10 ± 6.10 (32-53)	0	-
Score for control questions on faux pas stories (max 18)	18.00 ± 0.00 (18-18)	18.00 ± 0.00 (18-18)	0	-
Score for control questions on control stories (max 18)	17.80 ± 0.42 (17-18)	17.90 ± 0.32 (17-18)	2	8, 10
Number of correctly identified faux pas stories (max 9)	8.50 ± 0.71 (7-9)	7.90 ± 1.10 (6-9)	0	-
% of correctly identified faux pas stories	87.59 ± 12.19 (70-100)	85.37 ± 11.30 (59-98)	0	-
Number of correctly identified control stories	7.40 ± 1.51 (5-9)	7.80 ± 1.32 (5-9)	1	8
Number of control stories discarded for incorrectly answered control questions	0.20 ± 0.42 (0-1)	0.20 ± 0.42 (0-1)	0	-
% of correctly identified control stories	83.75 ± 14.84 (63-100)	87.64 ± 14.29 (56-100)	0	-
Number of faux pas stories where they correctly identified the person committing the faux pas	8.50 ± 0.71 (7-9)	7.80 ± 1.23 (5-9)	0	-
Number of faux pas stories where they correctly identified “why x shouldn’t have said…”	8.00 ± 1.05 (6-9)	8.00 ± 1.05 (6-9)	0	-
Number of faux pas stories where	6.80 ± 3.19	7.50 ± 0.97	2	8, 10

they correctly identified "why x said it…"	(0-9)	(6-9)		
Number of faux pas stories where they correctly answered "did x know that y?"	7.20 ± 1.87 (4-9)	6.20 ± 1.87 2-8	0	-
Number of faux pas stories where they correctly answered "How did x feel?"	8.30 ± 0.68 (7-9)	7.80 ± 1.23 (5-9)	0	-

Table 12: Atypical responses given to control questions by patient eight and patient ten.

Story no.	Question	Response
Responses from patient eight[a]		
2	4 Why do you think Sarah said it?	"To get one over on Helen"
4	4 Why do you think Lisa said it?	"Just to irritate her friend"
7	4 Why do you think Mary said it?	"Maybe she wanted a little boy"
12	4 Why do you think Joe said it?	"He was trying to be top dog"
13 & 14	4 Why do you think X said it?	"Don't know"
15	4 Why do you think Jake said it?	"To get one over on Christine"
18	4 Why do you think Claire said it?	"Trying to be smart"

Responses from patient ten		
2	4 Why do you think Sarah said it?	Thought that "Sarah spilled the coffee on the dress on purpose, so she could bring up the party and spoil the surprise for Helen. Or to cause friction."
2	6 How do you think Helen felt?	Thought that Sarah was "only concerned about herself because she focused on the dress rather than the party."
4	4 Why do you think Lisa said it?	"She was jealous of Gill and trying to be catty."
11	4 Why do you think Joe said it?	He thought that Jo said it because he "felt jealous of Mike and didn't want him taking over his position in the school." He thought it was deliberate.
15	4 Why do you think Jake said it?	He thought that Jake said it intentionally to put one over and put Christine down.
16	4 Why do you think Tim said it?	"Trying to get some attention and create a scene." Assumed that Tim could see Jack was waiting to pay.
18	4 Why do you think Claire said it?	"Clare said it to cause problems."

[a] Patient eight was severally dysarthric, the responses listed above were given using a light writer and therefore are relatively brief.

Graded Naming Test

Patient and control groups were compared on their Graded Naming Test scores. Comparison of the mean, standard deviation and range of scores on the Graded Naming Test indicated that both groups were relatively homogeneous. The mean score for the patient group was 24.20 with a standard deviation of 2.78 and scores ranging from 20–29. The mean score for the control group was 22.80 with a standard deviation of 4.30 and scores ranging from 13–27. A *t* test showed no significant difference between the two groups ($t(18)=-0.862$ $p\geq0.05$). A percentile analysis

comparing the scores of patients with the distribution of scores for controls did not identify any patients out with the normal distribution for the controls. All participants were able to complete the graded naming test.

Discussion

Measures of cognitive function sensitive to changes in the orbitofrontal cortex

1 Iowa Gambling Task

This study did not find a significant difference between patient and control groups for any of the IOGT variables. However, the differences shown, though not significant are in line with our hypothesis. The percentile analysis identified at least three individuals with ALS who appeared to show cognitive difficulties including perseveration, which impaired their performance relative to controls. Patients six, nine and 10 were out with the normal distribution for control participants for selections of good decks and selections of bad decks. As cognitive changes in ALS are thought to be subtle and do not occur in all individuals, the IOGT may not be sensitive enough to detect cognitive changes in this type of small sample where only some of the patient group exhibit cognitive changes. The difficulties shown by patients six, nine and 10 are in line with the deficits found by Bechara et al. (2000).

The version of the IOGT used was designed to give increasing delayed punishment, for instance the magnitude of punishment received from a particular deck increases as participants select more cards from that deck (see Table 7). Selections from decks A and B will give the same amount of financial punishment over 60 trials, Deck A punishes frequently in small amounts and deck B punishes less frequently in large amounts. Decks C and D will also give the same financial punishment over 60 trials, deck C punishing frequently in small amounts and deck D punishes infrequently in larger amounts (see Table 7). This study was concerned with whether cognitive changes known to be linked to the OFC were present in patients with ALS whereas Bechara et al. (2000) focused on trying to explain the cognitive processes responsible for the deficits shown on

the IOGT. The modification made to the IOGT which gave increasingly severe punishment in later selections was introduced by Bechara et al. (2000) in order to test whether insensitivity to reward or hypersensitivity to punishment were appropriate explanations. Future research with ALS patients could use a version of the IOGT which did not increase the severity of punishment with later deck selections. Figures 2-7 show that for block 5, participants changed their deck selections as the punishment was increased. Removing this modification would make results more comparable across all five blocks. Figures 2-7 also show that selections for block 1 were not particularly representative of overall performance. The addition of a series of practice trials to the IOGT could help to ensure that selections were more comparable across all five blocks.

There is still some debate regarding the exact cognitive changes which cause poor performance on the IOGT. Bechara et al. (2000) favour the somatic marker hypothesis and Rolls (1999, as cited in Bechara et al., 2000) has suggested that the evaluation and somatic tagging of possible future outcomes may occur in the OFC. Maia and McClelland (2004) claim to show that participants have a more conscious knowledge of the possible future outcomes in the IOGT and that this conscious knowledge could be what is guiding their performance rather than unconscious somatic markers. This claim in itself cannot however discount the somatic marker explanation, as the somatic marker hypothesis does not propose that this somatic tagging of representations of future consequences is an exclusively unconscious process (Bechara et al., 2005). Maia and McClelland (2005) have responded to this by indicating that their findings suggest that somatic markers are not necessary for success on the IOGT. It should be noted that Maia and McClelland (2004) assessed the performance of normal individuals who were able to successfully identify advantageous outcomes. Both Bechara et al., 2000 and this study have focused on identifying individuals who fail the IOGT and propose that this failure is due to orbitofrontal dysfunction. As the use of the IOGT in this study was to assess its ability to detect cognitive change in ALS and the recent debate regarding the validity of the somatic marker hypothesis regards normal participants who are able to successfully identify advantageous

outcomes, the finer points of this debate only have a direct bearing on future research with ALS if research into the cognitive processes underlying performance on the IOGT indicates that the IOGT can be failed without impairment of somatic tagging and therefore without orbitofrontal dysfunction. To date this has not been demonstrated. It will be interesting to see how the findings of Maia and McClelland (2004) are pursued, particularly in regards to individuals who show impairments on the IOGT.

2 Visual Discrimination Learning Task

For this task, a group difference was found between patients and controls for the number of errors between the first and second criterion and the number of trials between the first and second criterion. This difference was in the opposite direction to that predicted in that patients took more trials than controls between the first and second criterion. No other significant differences were found. It appears that the VDLT was not particularly suited to identifying cognitive changes in our patient group compared to the control group. During this study several methodological shortcomings of the VDLT became apparent. Throughout testing it was apparent for both patients and controls that most participants did not have any overt awareness of which stimulus fractal pattern was rewarding or punishing. Consequently participants tended to make selections at random. It appeared that many of the participants who reached criterion one or two times did so by chance, and did not realise that contingencies had been changed. The results of the IOGT indicate that participants could identify that selections from some decks were rewarding and others punishing. The results from the VDLT did not show any pattern indicating that participants on the whole had this kind of awareness either consciously or otherwise. There are several modifications to the VDLT which may make this task more sensitive. Future modifications could include increasing the difference between the punishment and reward ranges used so that it was more obvious to participants which stimulus was punishing and which rewarding. Punishment/reward ranges similar to those used in the IOGT could be used. During the VDLT some participants appeared to select a stimulus accidentally as they were unaware of when the

pictures would swap positions. In future the VDLT could be modified to always present the two fractal pictures in the same position e.g. upper fractal pattern or lower fractal pattern.

For participants who did not reach criterion more than once it was thought to be better to exclude them from analysis for "Number of trials between first and second criterion", "Number of errors between first and second criterion" and "Number of the last error trial before the second criterion" instead of using the number of trials or errors they made from the first criterion until the end of the test. This decision was made because there was no way of knowing how long these participants would have continued before reaching criterion. The decision to limit the VDLT to 100 trials was made to ensure that the testing session was not to long for participants. This limit was chosen because it is the same as they used for the IOGT, however no account was taken of the more subtle differences between the punishment and reward ranges in the VDLT compared to the IOGT. In future pilot testing, the VDLT to determine an appropriate number of trials to allow the test to run for would be advisable.

As with the IOGT a percentile analysis indicated that a minority of patients had cognitive difficulties with this task. In this sense our results are similar to previous findings, however the VDLT used in this study is not analogous to the one used in previous studies so no direct comparisons can be made. Additionally as there were missing cases and the sample size was reduced, these results may not be particularly representative. Future research using the VDLT could overcome this problem by increasing the maximum number of trials as described above.

3 Faux pas test

As the Faux Pas Test administered to our participants is not analogous to the one used in previous research with two questions removed and some questions reworded, our results are not directly comparable to those of Gregory et al. (2002) although the alterations made are unlikely to have changed our results. No significant differences were found between the patient and control

groups for all variables of the Faux Pas Test, however our results are do not contradict the findings of Gregory et al. (2002). They were testing patients with FTD known to show behavioural changes indicating of a lack of high level ToM knowledge. We tested a sample of ALS patients of whom we expected only a portion to show cognitive changes and furthermore to show cognitive changes in a less overt manner than individuals with FTD or with ALS dementia. It is therefore not surprising that the Faux Past Test was not sensitive enough to detect the cognitive changes in ALS non dementia patients. Table 11 indicates that all patients correctly identified at least seven faux pas stories, however this variable is only a representation of whether participants correctly answered question one, ”Did anyone say something they shouldn’t have said, or say something awkward?”. Knowing that a faux pas has occurred requires an understanding that the individual who said or did something offensive does not realise that their actions or words are offensive (Stone et al., 1998; Gregory et al., 2002). This means that answers to question four, “Why do you think X said it?”, give a more accurate indication of whether the participant could grasp the concept of a faux pas rather than merely realising that someone said something inappropriate.

Our results are in line with previous findings in that the atypical responses given to question four by patient eight and patient 10 are very similar to the responses given by patients with FTD and OFC damage reported in Stone and Baron-Cohen (2002) and Gregory et al. (2002). Before analysing the Faux Pas Test, it was decided to include the responses of patient eight and 10 (see Table 11) as they appeared to give atypical responses during testing, additionally patient eight and 10 were the only patients identified as abnormal by the percentile analysis. In the case of patient 10 despite perseveration shown on other tests and atypical answers to the faux pas stories his wife did not indicate that she had noticed any cognitive changes in him since the onset of MND. This indicates the subtle nature of cognitive changes shown in ALS non dementia patients. Consequently any future use of the Faux Pas Test with this patient group would be wise to take a larger sample of ALS patients and to select patients from within that sample suspected of

showing cognitive changes using a criteria similar this study's percentile analysis. This methodology would allow the Faux Pas Test to be put to better use with ALS non dementia patients in future. In this study number of patients who were thought to show cognitive changes was too small to conduct any further meaningful analysis on this subgroup. The deficits observed on the Faux Pas Test are consistent with the notion that the cognitive processes responsible for understanding ToM are part of a circuit and are not served by a single cognitive system or single brain area (Gregory et al., 2002; Stone et al., 1998). This circuit is thought to involve the OFC and it is possible that changes in the OFC could have lead to the atypical answers given in our study (Gregory et al., 2002; Stone et al., 1998). The results of this study are in line with the explanation outlined above.

Other measures of cognitive function

Written Verbal Fluency Index and Graded Naming Test

This study also investigated whether previously identified cognitive deficits of written verbal fluency and confrontation naming ability found in ALS co occur with deficits on tests sensitive to orbitofrontal dysfunction. Previous research with the WVFI identifying a deficit in ALS patients has proposed the following explanation. The WVFI task taxes executive resources such as employing and switching between different retrieval strategies to facilitate word generation. It is this ability to disengage and switch between retrieval strategies that is thought to be impaired in some ALS patients (Abrahams et al*.,* 2000). Our study failed to replicate previous findings of a written verbal fluency deficit. In our study, six patients were compared with ten controls as motor difficulties prevented four patients from completing the WVFI. The sample size for this comparison is probably too small to detect any meaningful difference. Furthermore, patient eight was one of the four who could not participate in the WVFI and this participant appeared to show deficits on several of the other tasks. Executive processes thought to be necessary for success on the WVFI are not necessarily the same processes which are affected in individuals who show impairments on the other tasks used in this study. The fact that we did not find a deficit on the

WVFI or GNT suggests the possibility that deficits on tasks that tap OFC functions may be independent of deficits on other tasks such as the WVFI and GNT. Future research comparing measures of orbitofrontal dysfunction with the WVFI would benefit from a larger sample to ensure a meaningful comparison can be made. An inherent difficulty with any research involving a written assessment in ALS is that the sample tested is never going to be representative of the whole group. Those who can't be tested have more severe motor difficulty and tend to be in the later stages of ALS.

General discussion

One would not expect that all types of cognitive change will have the same incidence and, if cognitive changes are present in an individual, these cognitive changes may be easier to detect in some modalities than others. As with nearly all psychological variables, what we measure with our tests and assessments is not an underlying variable. The Faux Pas Test does not give a direct measure of an individual's ToM knowledge and the IOGT and VDLT do not directly measure perseveration tendency or switching ability. Rather these tests all assess a behaviour that is thought to depend on these underlying variables. Consequently some types of test or assessment are more sensitive to detecting cognitive changes than others. For the IOGT, VDLT and the Faux Pas Test, it appears that cognitive changes were present in patients classified as abnormal by the percentile analysis, but that these changes were not present in a large enough number of patients to be identified as significant by the above tests. In particular, patient eight and patient 10 appear to show cognitive difficulties on all three of these tests.

Implications

If, after future research the incidence of orbitofrontal dysfunction in non demented individuals with ALS can be identified, it would be useful to alert carers and professionals to the possibility of cognitive difficulties or related behaviour change caused by orbitofrontal dysfunction. In particular, deficits on Theory of Mind tasks would be likely to have most impact. However, as

ALS is a progressively debilitating condition and responsibility for planning and carrying out daily activities tends to diminish for the patient, orbitofrontal dysfunction at the level detected in this study is unlikely to have a significant impact on patients themselves. It is possible that ALS non dementia patients who show cognitive changes such as the individuals identified by the percentile analysis could go on to develop concomitant FTD, however the quick progression of the disease and subsequent death would make this type of longitudinal comparison impractical. Further research would be better to focus on comparative cross sectional studies investigating the incidence and prevalence of cognitive changes in three groups, ALS non dementia, ALS dementia and FTD without ALS. As no cognitive deficits were found on the WVFI or the GNT it would be interesting to further investigate areas of cognitive function in which deficits in one area can be dissociated from deficits in another area in the group of ALS non dementia.

Conclusions

This study suggests that cognitive changes in ALS non dementia can involve orbitofrontal dysfunction as shown by the percentile analysis of defects on the IOGT, VDLT and Faux Pas Test. Of our sample of 10 ALD non dementia patients, two individuals, patient eight and patient 10, were found to show cognitive changes indicative of orbitofrontal dysfunction on all three measures. As no deficits were evident on the WVFI or the GNT it is concluded that cognitive changes indicative of orbitofrontal dysfunction can occur without measurable cognitive changes affecting written verbal fluency and confrontation naming ability. This study recommends using a larger sample in order to allow comparisons between controls and patients thought to show cognitive changes rather than just comparisons between controls and the entire patient group.

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Appendices

Appendix one

Information sheets and consent forms used for controls and patients

Psychology
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Information Sheet for Control Participants

Study title: "Thinking and Behaviour in Motor Neurone Disease (MND)"

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Whilst it is known that MND only affects the motor neurons in the majority of cases, recent evidence has shown that there may be some involvement of other regions of the brain in a few sufferers. Using a battery of psychological tests and questionnaires we hope to investigate whether some sufferers of MND experience changes in their thinking and behaviour. These results will be compared to a group of participants such as yourself who do not have MND.

Why have I been chosen?

We will be seeing a total of 30 healthy control participants. We will also be seeing a total of 30 MND patients.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

If you decide to take part we will start by asking you several background questions. Then we will move on to a series of tests, similar to word games and puzzles, some of which will take place on a laptop computer.

During the testing we may sometimes ask to audio-record your voice whilst you are performing some of the tasks. We ensure that there will be nothing on the tape that could identify you in person and that these tapes will be destroyed once the data has been obtained.

The test battery 2 hours long, if you need a break at any time you are free to do so.

What do I have to do?

You will not have to take medication or undergo any invasive procedure whatsoever. Most tests are in the forms of interviews, questionnaires or “paper and pencil” tests.

What are the possible disadvantages and risks of taking part?

We do not anticipate any health risks from taking part in this study. If you feel distressed at any time during the interview it is important that you let the interviewer know straight away. If you feel distressed after the interview please contact Dr Sharon Abrahams 0131 650 3339.

What are the possible benefits of taking part?

There will be no direct benefit to you or your carer by taking part, and your individual results will not be revealed to you. However, we will make any future publications of the findings available to you. It is hoped that this research will improve our knowledge relating to MND and may influence care practices in the future.

What if something goes wrong?

Whilst we do not anticipate any adverse effects from taking part in this study, If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it. You will be allocated an anonymous ID code during testing which will be used in place of your name on any future publications.

What will happen to the results of the research study?

The results of the research will be published in appropriate peer-reviewed scientific journals for distribution to other healthcare professionals. Talks and presentations may be made at MNDA meetings and conferences. In all cases, your name and personal details will not be identified.

Who is organising the research?

The study is being organized by Dr. Sharon Abrahams, from the University of Edinburgh, in collaboration with Ms Judith Newton and Dr Richard Davenport at the Western General Hospital.

Who has reviewed the study?

This study has been granted ethics approval by the Lothian Research Ethics Committee.

Contact for Further Information

If you wish to ask anything further then please contact Dr Sharon Abrahams via the address below or on 0131 650 3339 (s.abrahams@ed.ac.uk), or Ms Judith Newton on 0131 537 2131 (judith.newton@luht.scot.nhs.uk)

Dr Sharon Abrahams
Department of Psychology, PPLS
7 George Square
Edinburgh, EH8 9JZ

Thank you for reading this information sheet. You will be given a copy to keep. If you have understood the contents of this sheet and wish to take part, please complete the consent sheet on the next page. If you have any questions please feel free to ask them now.

Control Identification Number for this trial:

CONSENT FORM

Title of Project: "Thinking and Behaviour in MND"

Name of Researcher: Dr Sharon Abrahams

Please initial box

❑ I confirm that I have read and understand the information sheet dated ..... (version .....) for the above study and have had the opportunity to ask questions.

❑ I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

❑ I understand that my voice may be audiotaped for the purpose of the study

❑ I agree to take part in the above study.

_____	_____	
Name of Participant	Signature	Date
_____	_____	
Researcher	Signature	Date

1 for control; 1 for researcher

Psychology
SCHOOL *of* PHILOSOPHY, PSYCHOLOGY *and* LANGUAGE SCIENCES

The University of Edinburgh
7 George Square
Edinburgh EH8 9JZ

Telephone 0131 650 3440
or direct dial 0131 650
Fax 0131 650 3461
Email Psychology@ed.ac.uk

Information Sheet for People with MND

Study title: "Thinking and Behaviour in Motor Neurone Disease (MND)"

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Whilst it is known that MND only affects the motor neurons in the majority of cases, recent evidence has shown that there may be some involvement of other regions of the brain in a few sufferers. Using a battery of psychological tests and questionnaires we hope to investigate whether some sufferers of MND experience changes in their thinking and behaviour. These results will be compared to a group of participants who do not have MND.

Why have I been chosen?

We believe this is a suitable study for you, if you would like to take part. We will be seeing a total of 30 MND patients. We will also be seeing a total of 30 healthy control participants.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive, now or in the future.

What will happen to me if I take part?

Testing can take place at your home at a time of your convenience, or at the Department of Psychology, University of Edinburgh, 7 George Square if you prefer. If you decide to take part we will start by asking you some questions about the duration of your symptoms and how they are affecting you at present. Then we will move on to a series of tests, similar to word games and puzzles, some of which will take place on a laptop computer.

During the testing we may sometimes ask to audio-record your voice whilst you are performing some of the tasks. We ensure that there will be nothing on the tape that could identify you in person and that these tapes will be destroyed once the data has been obtained.

As part of the study, we would separately like to ask a carer or relative who knows you well some questions. We are interviewing carers to try and get as many perspectives as possible on changes in behaviour that may, or may not occur in people with MND. This will consist of them having a brief interview that will enquire about any changes that may have occurred since the onset of your MND, and they will also be asked to complete some questionnaires. This will take up to half an hour and will be carried out whilst you are carrying out one of the tests. Any responses given to us by your carer will remain confidential and we will not reveal them to you. You will also be asked to fill out a version of these questionnaires related to any changes you may have noticed yourself. We will not tell your carer how you responded to any of the questionnaires.

The test battery 2 hours, but this can be split into two shorter sessions if you prefer and if you need to take a break at any time you are free to do so.

What do I have to do?

You will not have to come off medication or undergo any invasive procedure whatsoever. Most tests are in the forms of interviews, questionnaires or puzzle-like tests. If you are unable to write we will assist you in filling out the questionnaires. If you are unable to speak we may skip certain tests that rely on spoken answers.

What are the possible disadvantages and risks of taking part?

We do not anticipate any health risks from taking part in this study. Due to the length of the battery you may find testing to be tiring. If you think this will be the case we recommend splitting the testing into two shorter sessions at your convenience, morning or afternoon. You will not be identified in our computers or publications by name, but by subject number, and all information will be kept strictly confidential.

If you feel distressed at any time during the interview it is important that you let the interviewer know straight away. If you feel distressed after the interview please contact Ms Judith Newton, MND Nurse Specialist on 0131 537 2131 or Dr Sharon Abrahams 0131 650 3339.

What are the possible benefits of taking part?

There will be no direct benefit to you or your carer by taking part, and your individual results will not be revealed to you. However, we will make any future publications of the findings available to you. It is hoped that this research will improve our knowledge relating to MND and may influence care practices in the future.

What if something goes wrong?

Whilst we do not anticipate any adverse effects from taking part in this study, If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it. You will be allocated an anonymous ID code during testing which will be used in place of your name on any future publications.

What will happen to the results of the research study?

The results of the research will be published in appropriate peer-reviewed scientific journals for distribution to other healthcare professionals. Talks and presentations may be made at MNDA meetings and conferences. In all cases, your name and personal details will not be identified.

Who is organising and funding the research?

The study is being organized by Dr. Sharon Abrahams, from the University of Edinburgh, in collaboration with Ms Judith Newton and Dr Richard Davenport at the Western General Hospital.

Who has reviewed the study?

This study has been granted ethics approval by the Lothian Research Ethics Committee.

Contact for Further Information

If you wish to ask anything further then please contact Dr Sharon Abrahams via the address below or on 0131 650 3339 (s.abrahams@ed.ac.uk), or Ms Judith Newton on 0131 537 2131 (judith.newton@luht.scot.nhs.uk)

Dr Sharon Abrahams
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Thank you for reading this information sheet. You will be given a copy to keep. If you have understood the contents of this sheet and wish to take part, please complete the consent sheet on the next page. If you have any questions please feel free to ask them now.

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: "Thinking and Behaviour in MND"

Name of Researcher: Dr Sharon Abrahams

Please initial box

☐ I confirm that I have read and understand the information sheet dated ..... (version .....) for the above study and have had the opportunity to ask questions.

☐ I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

☐ I understand that my voice may be audiotaped for the purpose of the study

☐ I understand that sections of any of my medical notes may be looked at by responsible individuals from King's College Hospital, London or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

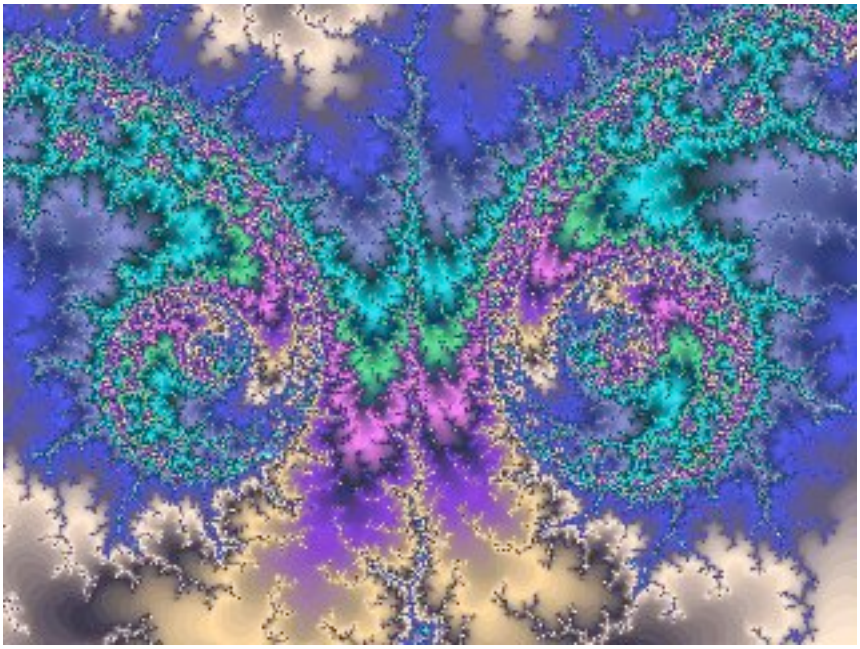
☐ I agree to take part in the above study.

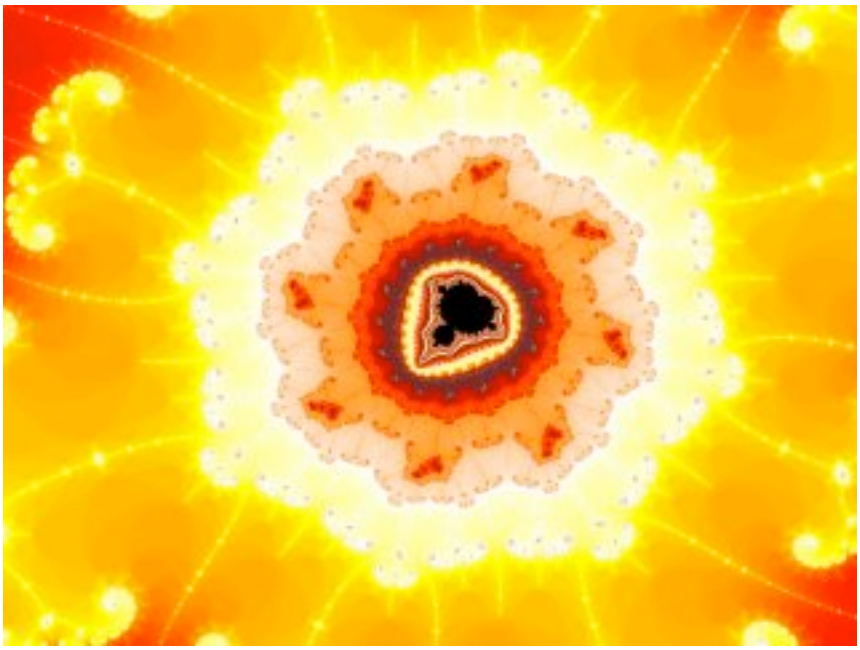
_____	_____	
Name of Patient	Signature	Date
_____	_____	
Witness (if unable to write)	Signature	
_____	_____	
Researcher	Signature	Date

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix two

Fractal patterns used in the VDLT





Appendix three

Faux pas stories used for the Faux Pas Test with all changes, along with faux pas questions and control questions for each story.

V. Stone FP test
S.Baron-Cohen

1. Vicky was at a party at her friend Oliver's house. She was talking to Oliver when another woman came up to them. She was one of Oliver's neighbors. The woman said, "Hello," then turned to Vicky and said, " I don't think we've met. I'm Maria, what's your name?" "I'm Vicky." "Would anyone like something to drink?" Oliver asked.

Did anyone say something they shouldn't have said or something awkward?

If no skip to control questions.

Incorrect: Yes *score points* *Correct*: No *score points*

score 2 points if they get it correct that no one said anything they shouldn't have said, 0 if they say someone said something they shouldn't have said

If yes, ask:
Who said something they shouldn't have said or something awkward?

Why shouldn't he/she have said it or why was it awkward?

Why do you think he/she said it?

Did Oliver know that Vicky and Maria did not know each other?

How do you think Vicky felt?

Control questions: In the story, where was Vicky? *point*

Did Vicky and Maria know each other? *point*

2. Helen's husband was throwing a surprise party for her birthday. He invited Sarah, a friend of Helen's, and said, "Don't tell anyone, especially Helen." The day before the party, Helen was over at Sarah's and Sarah spilled some coffee on a new dress that was hanging over her chair. "Oh!" said Sarah, "I was going to wear this to your party!" "What party?" said Helen. "Come on," said Sarah, "Let's go see if we can get the stain out."

Did anyone say something they shouldn't have said or something awkward?

If no skip to control questions.

Correct: Yes *Incorrect*: No

If yes, ask:
Who said something they shouldn't have said or something awkward?

Why shouldn't *Sarah* have said it or why was it awkward?

Why do you think *Sarah* said it?

Did Sarah remember that the party was a surprise party?

How do you think Helen felt?

Control question: In the story, who was the surprise party for?

What got spilled on the dress?

3. Jim was shopping for a shirt to match his suit. The salesman showed him several shirts. Jim looked at them and finally found one that was the right colour. But when he went to the dressing room and tried it on, it didn't fit. "I'm afraid it's too small," he said to the salesman. "Not to worry," the salesman said. "We'll get some in next week in a larger size." "Great. I'll just come back then," Jim said.

Did anyone say something they shouldn't have said or something awkward?

If no skip to control questions.

Incorrect: Yes *score points* *Correct*: No *score points*

If yes, ask:
Who said something they shouldn't have said or something awkward?

Why shouldn't he/she have said it or why was it awkward?

Why do you think he/she said it?

When he tried on the shirt, did Jim know they didn't have it in his size?

How do you think Jim felt?

Control question: In the story, what was Jim shopping for? *point*

Why was he going to come back next week? *point*

4. Jill had just moved into a new flat. Jill went shopping and bought some new curtains for her bedroom. When she had just finished decorating the flat, her best friend, Lisa, came over. Jill gave her a tour of the flat and asked, "How do you like my bedroom?" "Those curtains are horrible," Lisa said. "I hope you're going to get some new ones!"

Did anyone say something they shouldn't have said or something awkward?

If no skip to control questions.

Correct: Yes *Incorrect*: No

If yes, ask:
Who said something they shouldn't have said or something awkward?

Why shouldn't *Lisa* have said it or why was it awkward?

Why do you think *Lisa* said it?

Did Lisa know who had bought the curtains?

How do you think Jill felt?

Control question: In the story, what had Jill just bought?

How long had Jill lived in this flat?

5. Bob went to the barber for a haircut. "How would you like it cut?" the barber asked. "I'd like the same style as I have now, only take about an inch off," Bob replied. The barber cut it a little uneven in the front, so he had to cut it shorter to even it out. "I'm afraid it's a bit shorter than you asked for," said the barber. "Oh well," Bob said, "it'll grow out."

Did anyone say something they shouldn't have said or something awkward?

If no skip to control questions.

Incorrect: Yes *score points* *Correct*: No *score points*

If yes, ask:
Who said something they shouldn't have said or something awkward?

Why shouldn't he/she have said it or why was it awkward?

Why do you think he/she said it?

While he was getting the haircut, did Bob know the barber was cutting it too short?

How do you think Bob felt?

Control question: In the story, how did Bob want his hair cut? *point*

How did the barber cut his hair? *point*

6. John stopped off at the petrol station on the way home to fill up his car. He gave the cashier his credit card. The cashier ran it through the machine at the counter. "I'm sorry," she said, "the machine won't accept your card." "Hmmm, that's funny," John said. "Well, I'll just pay in cash." He gave her twenty pounds and said, "I filled up the tank with unleaded."

Did anyone say something they shouldn't have said or something awkward?

If no skip to control questions.

Incorrect: Yes *score points* *Correct*: No *score points*

If yes, ask:
Who said something they shouldn't have said or something awkward?

Why shouldn't he/she have said it or why was it awkward?

Why do you think he/she said it?

When he handed his card to the cashier, did John know the machine wouldn't take his card?

How do you think John felt?

Control question: In the story, what did John stop off to buy? *point*

Why did he pay in cash? *point*

7. Sally is a three-year-old girl with a round face and short blonde hair. She was at her Aunt Carol's house. The doorbell rang and her Aunt Carol answered it. It was Mary, a neighbour. "Hi," Aunt Carol said, "Nice of you to stop by." Mary said, "Hello," then looked at Sally and said, "Oh, I don't think I've met this little boy. What's your name?"

Did anyone say something they shouldn't have said or something awkward?

If no skip to control questions.

Correct: Yes *Incorrect*: No

If yes, ask:
Who said something they shouldn't have said or something awkward?

Why shouldn't *Mary* have said it or why was it awkward?

Why do you think *Mary* said it?

Did Mary know that Sally was a girl?

How do you think Sally felt?

Control question: In the story, where was Sally? *point*

Who came to visit? *point*

8. Joan took her dog, Zack, out to the park. She threw a stick for him to chase. When they had been there a while, Pam, a neighbour of hers, passed by. They chatted for a few minutes. Then Pam asked, "Are you heading home? Would you like to walk together?" "Sure," Joan said. She called Zack, but he was busy chasing pigeons and didn't come. "It looks like he's not ready to go," she said. "I think we'll stay." "OK," Pam said. "I'll see you later."

Did anyone say something they shouldn't have said or something awkward?

If no skip to control questions.

Incorrect: Yes *score points* *Correct*: No *score points*

If yes, ask:
Who said something they shouldn't have said or something awkward?

Why shouldn't he/she have said it or why was it awkward?

Why do you think he/she said it?

When she invited her, did Pam know that Joan wouldn't be able to walk home with her?

How do you think Pam felt?

Control question: In the story, where had Joan taken Zack? *point*

Why didn't she walk with her friend Pam? *point*

9. Joanne had had a major role in last year's school play and she really wanted the lead role this year. She took acting classes, and in the spring, she auditioned for the play. The day the decisions were posted, she went before class to check the list of who had made the play. She hadn't made the lead and had instead been cast in a minor role. She ran into her boyfriend in the hall and told him what had happened. "I'm sorry," he said. "You must be disappointed." "Yes," Joanne answered, "I have to decide whether to take this role."

Did anyone say something they shouldn't have said or something awkward?

If no skip to control questions.

Incorrect: Yes *score points* *Correct*: No *score points*

If yes, ask:
Who said something they shouldn't have said or something awkward?

Why shouldn't he/she have said it or why was it awkward?

Why do you think he/she said it?

When he first ran into her in the hall, did Joanne's boyfriend know that she hadn't gotten the role?

How do you think Joanne felt?

Control question: In the story, what role did Joanne get?

What kind of role had she had the previous year? *point*

What did her boyfriend say? *point*

10. Joe was at the library. He found the book he wanted about hiking in the Grand Canyon and went up to the front counter to check it out. When he looked in his wallet, he discovered he had left his library card at home. "I'm sorry," he said to the woman behind the counter. "I seem to have left my library card at home." "That's OK," she answered. "Tell me your name, and if we have you in the computer, you can check out the book just by showing me your driver's license."

Did anyone say something they shouldn't have said or something awkward?

If no skip to control questions.

Incorrect: Yes *score points* *Correct*: No *score points*

If yes, ask:
Who said something they shouldn't have said or something awkward?

Why shouldn't he/she have said it or why was it awkward?

Why do you think he/she said it?

When Joe went into the library, did he realize he didn't have his library card?

How do you think Joe felt?

Control question: In the story, what book did Joe get at the library? *point*

Was he going to be able to check it out? *point*

12. Mike, a nine-year-old boy, just started at a new school. He was in one of the cubicles in the toilets at school. Joe and Peter, two other boys, came in and were standing at the sinks talking. Joe said, "You know that new guy in the class? His name's Mike. Doesn't he look weird? And he's so short!" Mike came out of the cubicle and Joe and Peter saw him. Peter said, "Oh hi, Mike! Are you going out to play football now?"

Did anyone say something they shouldn't have said or something awkward?

If no skip to control questions.

Correct: Yes *Incorrect*: No

If yes, ask:
Who said something they shouldn't have said or something awkward?

Why shouldn't *Joe* have said it or why was it awkward?

Why do you think *Joe* said it?

When Joe was talking to Peter, did he know that Mike was in one of the cubicles?

How do you think Mike felt?

Control question: In the story, where was Mike while Joe and Peter were talking?

What did Joe say about Mike?

13. Kim's cousin, Scott, was coming to visit and Kim made an apple pie especially for him. After dinner, she said, "I made a pie just for you. It's in the kitchen." "Mmmm," replied Scott, "It smells great! I love pies, except for apple, of course."

Did anyone say something they shouldn't have said or something awkward?

If no skip to control questions.

Correct: Yes *Incorrect*: No

If yes, ask:
Who said something they shouldn't have said or something awkward?

Why shouldn't *Scott* have said it or why was it awkward?

Why do you think *Scott* said it?

When he smelled the pie, did Scott know it was an apple pie?

How do you think Kim felt?

Control question: In the story, what kind of pie did Kim make?

How did Kim and Scott know each other?

14. Jeanette bought her friend, Anne, a crystal bowl for a wedding gift. Anne had a big wedding and there were a lot of presents to keep track of. About a year later, Jeanette was over one night at Anne's for dinner. Jeanette dropped a wine bottle by accident on the crystal bowl and the bowl shattered. "I'm really sorry. I've broken the bowl," said Jeanette. "Don't worry," said Anne. "I never liked it anyway. Someone gave it to me for my wedding."

Did anyone say something they shouldn't have said or something awkward?

If no skip to control questions.

Correct: Yes *Incorrect*: No

If yes, ask:
Who said something they shouldn't have said or something awkward?

Why shouldn't *Anne* have said it or why was it awkward?

Why do you think *Anne* said it?

Did Anne remember that Jeannette had given her the bowl?

How do you think Jeanette felt?

Control question: In the story, what did Jeanette give Anne for her wedding?

How did the bowl get broken?

15. At Fernhaven Primary School, there was a story competition. Everyone was invited to enter. Several of the primary 6 children did so. Christine, in primary 6, loved the story she had entered in the competition. A few days later, the results of the competition were announced: Christine's story had not won anything and a classmate, Jake, had won first prize. The following day, Christine was sitting on a bench with Jake. They were looking at his first prize trophy. Jake said, "It was so easy to win that contest. All of the other stories in the competition were terrible." "Where are you going to put your trophy?" asked Christine.

Did anyone say something they shouldn't have said or something awkward?

If no skip to control questions.

Correct: Yes *Incorrect*: No

If yes, ask:
Who said something they shouldn't have said or something awkward?

Why shouldn't *Jake* have said it or why was it awkward?

Why do you think *Jake* said it?

Did Jake know that Christine had entered a story in the contest?

How do you think Christine felt?

Control question: In the story, who won the contest?

Did Christine's story win anything?

16. Tim was in a restaurant. He spilled some coffee on the floor by accident. "I'll get you another cup of coffee," said the waiter. The waiter was gone for a while. Jack was another customer in the restaurant, standing by the cashier waiting to pay. Tim went up to Jack and said, "I spilled coffee over by my table. Can you mop it up?"

Did anyone say something they shouldn't have said or something awkward?

If no skip to control questions.

Correct: Yes *Incorrect*: No

If yes, ask:
Who said something they shouldn't have said or something awkward?

Why shouldn't *Tim* have said it or why was it awkward?

Why do you think *Tim* said it?

Did Tim know that Jack was another customer?

How do you think Jack felt?

Control question: In the story, why was Jack standing by the cashier?

What did Tim spill?

17. Eleanor was waiting at the bus stop. The bus was late and she had been standing there a long time. She was 65 and it made her tired to stand for so long. When the bus finally came, it was crowded and there were no seats left. She saw a neighbour, Paul, standing in the aisle of the bus. "Hello, Eleanor," he said. "Were you waiting there long?" "About 20 minutes," she replied. A young man who was sitting down got up. "would you like my seat?"

Did anyone say something they shouldn't have said or something awkward?

If no skip to control questions.

Incorrect: Yes *score points* *Correct*: No *score points*

If yes, ask:
Who said something they shouldn't have said or something awkward?

Why shouldn't he/she have said it or why was it awkward?

Why do you think he/she said it?

When Eleanor got on the bus, did Paul know how long she had been waiting?

How do you think Eleanor felt?

Control question:
In the story, why was Eleanor waiting at the bus stop for 20 minutes? *point*

Were there any seats available on the bus when she got on? *point*

18. Roger had just started work at a new office. One day, in the coffee room, he was talking to a new friend, Andrew. "What does your wife do?" Andrew asked. "She's a lawyer," answered Roger. A few minutes later, Claire came into the coffee room looking irritated. "I just had the worst phone call," she told them. "Lawyers are all so arrogant and greedy. I can't stand them." "Do you want to come look over these reports?" Andrew asked Claire. "Not now," she replied, "I need my coffee."

Did anyone say something they shouldn't have said or something awkward?

If no skip to control questions.

Correct: Yes *Incorrect*: No

If yes, ask:
Who said something they shouldn't have said or something awkward?

Why shouldn't *Claire* have said it or why was it awkward?

Why do you think *Claire* said it?

Did Claire know that Roger's wife was a lawyer?

How do you think Roger felt?

Control question: In the story, what does Roger's wife do for a living?

Where were Roger and Andrew talking?

19. Richard bought a new car, a red Peugeot. A few weeks after he bought it, he backed it into his neighbour Ted's car, an old beat-up Volvo. His new car wasn't damaged at all and he didn't do much damage to Ted's car either -- just a scratch in the paint above the wheel. Still, he went up and knocked on the door. When Ted answered, Richard said, "I'm really sorry. I've just put a small scratch on your car." Ted looked at it and said, "Don't worry. It was only an accident."

Did anyone say something they shouldn't have said or something awkward?

If no skip to control questions.

Incorrect: Yes *score points* *Correct*: No *score points*

If yes, ask:
Who said something they shouldn't have said or something awkward?

Why shouldn't he/she have said it or why was it awkward?

Why do you think he/she said it?

Did Richard know what his neighbour Ted's reaction would be?

How do you think Ted felt?

Control question: In the story, what did Richard do to Ted's car? *point*

How did Ted react? *point*

Abbreviations used in this study

amyotrophic lateral sclerosis	ALS
dorso-lateral pre-frontal cortex	DLPFC
Frontotemporal Dementia	FTD
functional Magnetic Resonance Imaging	fMRI
Graded Naming Tests	GNT
Intelligence Quotient	IQ
Iowa Gambling Task	IOGT
lower motor neurone	LMN
Motor neurone disease	MND
National Adult Reading Test, second edition	NART
orbitofrontal cortex	OFC
positron emission tomography	PET
regional cerebral blood flow	RCBF
superoxide dismutase one	SOD1
Theory of Mind	ToM
upper motor neurone	UMN
ventro-medial pre-frontal cortex	VMPFC
Visual discrimination Learning Task	VDLT
written verbal fluency	WVF
Written Verbal Fluency Index	WVFI